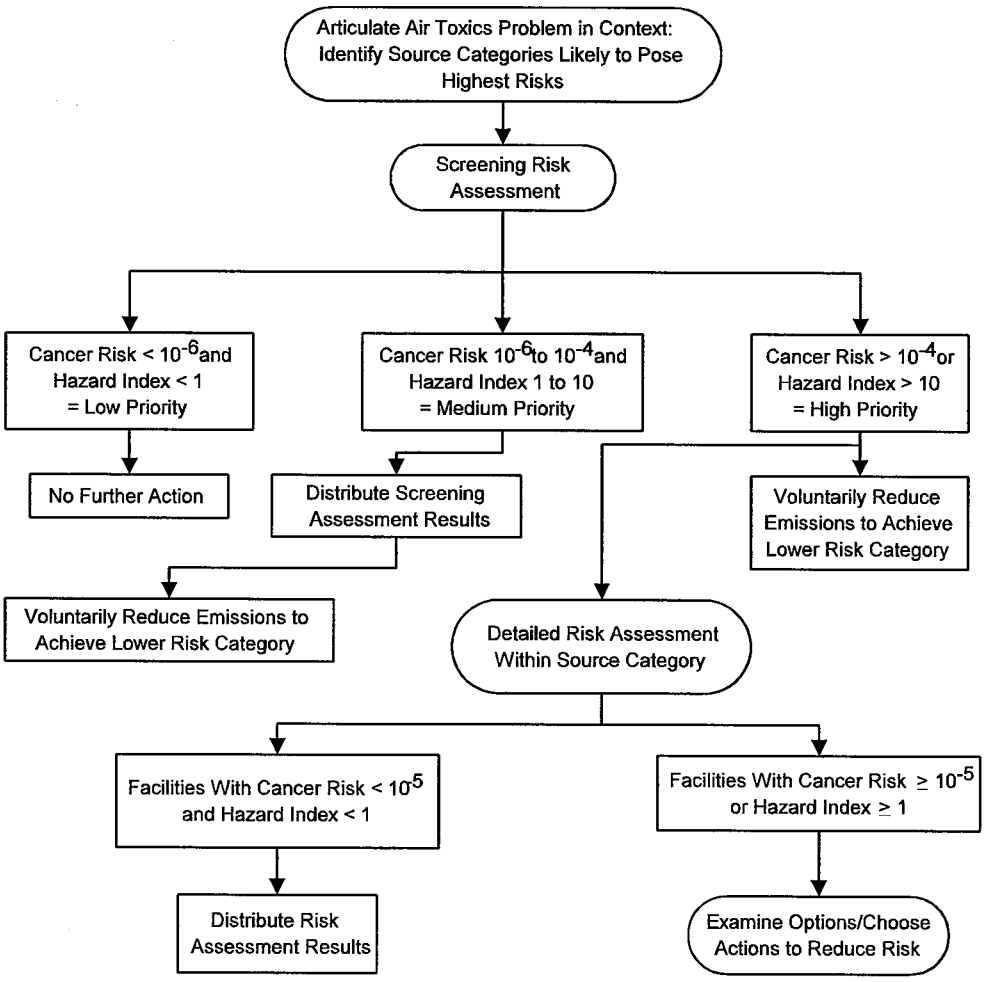
EXHIBIT 4
CRARM's RESIDUAL RISK RECOMMENDATIONS FOR AIR TOXICS



Source: CRARM 1997b

documents from these hearings were collectively referred to as the "Cancer Principles." Criticisms of these documents, which were inadvertently perceived as a formal Agency cancer risk assessment policy, led to the development of interim guidelines published by EPA in 1976. Three years later, the Interagency Regulatory Liaison Group (a conglomeration of several federal agencies, including EPA) published additional cancer risk assessment guidelines. At about the same time, cancer risk assessment techniques were used by EPA in the regulation of toxic chemicals under the 1976 Toxic Substances Control Act, and by the end of EPA's first decade,

risk assessment techniques were being used to develop water quality criteria for protection of human health. Throughout the 1980s, the use of risk assessment in EPA grew significantly and increasingly covered non-cancer risks in addition to cancer risks. During the 1980s, cancer risk assessment techniques were used in the development of national emission standards for air toxics such as vinyl chloride and benzene.

As the use of risk assessment increased in the 1980s, there was a growing awareness of both the lack of standard guidance for and the inconsistencies in the use of risk assessment at EPA. To address this need, the Agency undertook some administrative reforms and published several key guidelines and other policy documents, particularly during the second half of the decade. In response to the 1983 NRC report discussed in Section 3.1.1, the Agency published *Risk Assessment and Management: Framework for Decision Making* (EPA 1984), designed to address NRC recommendations and help EPA make better and more rapid decisions about environmental toxic chemical problems. Beginning in 1986, EPA has published an influential series of Agency-wide guidelines in the *Federal Register* identifying the recommended methods for assessing human health risks from environmental pollution. These guidelines (see text box), which cover both cancer and non-cancer risks, are not meant to be static but may be revised as new information and methods become available. EPA's use and development of human health risk assessment has continued to grow through the 1980s and 1990s with establishment of the Integrated Risk Information System (IRIS) toxicity data base, the repository of Agency consensus non-cancer RfDs and RfCs and cancer assessments.

EPA HUMAN HEALTH RISK ASSESSMENT GUIDELINES

EPA has published final risk assessment guidelines that address the following areas:

- Mutagenicity (EPA 1986a)
- Carcinogenicity (EPA 1986b)
- Chemical mixtures (EPA 1986c)
- Developmental toxicity (EPA 1991)
- Exposure assessment (EPA 1992a)
- Risk characterization (EPA 1995a)
- Reproductive toxicity (EPA 1996c)
- Probabilistic analysis (EPA 1997c)
- Neurotoxicity (EPA 1998c)

Draft revisions have been issued for carcinogenicity (EPA 1996b) and are under development for mixtures (EPA 1997d).

Since 1996, EPA has published draft revisions to its carcinogenicity guidelines (EPA 1996b) and is developing revisions to its mixtures guidelines (EPA 1997d). Revisions made to these guidance documents as a result of increased knowledge are designed to accommodate and reflect recent changes in the state-of-the-science for risk assessment. Some revised guidelines explicitly accommodate the replacement of default assumptions when supported by scientifically sound information (e.g., the 1996 proposed revisions to the cancer risk assessment guidelines). Human health risk assessment techniques embodied in these Agency-wide guidance documents are the foundation of the estimation of residual risks from air toxics under the CAA.

3.1.4 Development of Ecological Risk Assessment at EPA

The development of ecological risk assessment at EPA began in the 1970s primarily in two program areas, water quality and pesticide registration. The 1972 Clean Water Act (CWA) set objectives for eliminating surface water pollution based on receiving water uses of "fishable, swimmable waters." The 1972 amendments to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) required that pesticides be evaluated for "any unreasonable adverse effects on the environment." Subsequent legislation for environmental protection resulted in the development of other lines of ecological assessment practices in the late 1970s and in the 1980s, each tailored to the mandates of particular statutes (e.g., the Toxic Substances Control Act).

To meet its statutory mandates and promote consistency among assessments within program areas, EPA began developing program-specific guidelines for ecological assessments in the 1980s. Some of EPA's earliest ecological risk assessments were performed to meet the Agency's CWA mandate. NAS initiated the effort by publishing *Water Quality Criteria 1972* (the "Blue Book") (NAS 1973). In 1976, EPA published *Quality Criteria for Water* (the "Red Book") (EPA 1976). Then, in 1980, EPA published 64 individual ambient water quality criteria (AWQC) documents for pollutants listed as toxic in CWA section 307(a)(1) (EPA 1980). The process for deriving AWQC was formalized in 1986 when EPA published standardized guidelines on this subject (EPA 1986d). The guidelines specified that the criteria provide a "reasonable amount of protection of most species in an balanced healthy aquatic community" (EPA 1986d). For pesticide registration evaluations, EPA developed a framework for evaluating the effects of pesticides on nontarget organisms such as wildlife or aquatic communities and published these standard evaluation procedures in 1986 (EPA 1986e). Efforts to develop and document ecological assessment practices in other EPA program offices followed in the late 1980s (e.g., the *Risk Assessment Guidance for Superfund, Volume II: Environmental Evaluation Manual* (EPA 1989b)).

By the mid and late 1980s, EPA recognized a need for consistency in evaluating ecological risks across program offices and a need to make its ecological research efforts more responsive to ecological risk assessment needs Agency-wide. In response, the Office of Research and Development (ORD) began an evaluation of program-specific ecological risk assessment practices and initiated development of guidelines to establish a consistent and scientific basis for assessing ecological risks associated with toxic substances, for use Agency-wide. EPA's Risk Assessment Forum assumed responsibility for the Guidelines in 1990 and initiated three ecological risk guidance projects: (1) a "framework" to describe the basic principles for ecological risk assessment; (2) a set of case studies to illustrate the "state-of-the-practice" in ecological assessments; and (3) a long-range plan for developing specific ecological risk guidelines.

To accommodate the diverse kinds of ecological risk assessments conducted across program offices at EPA, the Agency found it necessary to modify the 1983 NRC paradigm for risk assessment. Most notably, EPA added a problem formulation phase to the beginning of the

ecological risk assessment process. In problem formulation, the scope, context, and ecological values of concern are identified. In 1992, EPA published its *Framework for Ecological Risk Assessment* (EPA 1992b). As the foreword of that document states, "use of the framework ... is not a requirement within EPA, nor is it a regulation of any kind. Rather, it is an interim product that is expected to evolve with use and discussion." As an interim method of providing more detailed guidance for its different program offices, EPA published two volumes of *A Review of Ecological Assessment Case Studies from a Risk Assessment Perspective* (EPA 1993a; EPA 1994b). The case studies are wide-ranging in scope, representing a variety of ecosystems, ecological endpoints, chemical and non-chemical stressors, and programmatic requirements within EPA, and illustrate how the *Framework* could be applied in each case.

As mentioned in Section 3.1.2, the CRARM discussed ecological risk assessment issues specific to air toxics risks and considered EPA's 1990 Framework document in their 1997 report (CRARM 1997a,b). CRARM recommended that EPA guidance include explicit involvement of stakeholders, particularly in the problem formulation stage, as well as a description of how ecological risk assessment measures and models should be selected.

In April 1998, EPA published its *Guidelines for Ecological Risk Assessment* (EPA 1998d), as a counterpart to the existing EPA health risk guidelines. The Guidelines, which expand upon and replace the widely used *Framework for Ecological Risk Assessment* (EPA 1992b), were developed to improve the quality of and consistency among EPA's ecological risk assessments. The guidelines are intentionally broad in scope in order to cover the full range of ecological risk assessment problems and do not provide detailed guidance. In the future, EPA plans to prepare more detailed guidance on specific areas of ecological risk assessment. The content and focus of the guidelines include the following.

- Ecological risk assessment is defined as a process for organizing and analyzing data, information, assumptions, and uncertainties to evaluate the likelihood of adverse ecological effects.

- Ecological risk assessments consist of three primary phases.

  - **Problem formulation** includes identifying goals and assessment endpoints, preparing a conceptual model, and developing an analysis plan. It is a formal process for generating and evaluating preliminary hypotheses about why ecological effects have occurred, or may occur, from human activities (EPA 1998d). It provides a foundation upon which the entire ecological risk assessment depends. However, because problem formulation is inherently interactive and iterative, rather than linear, substantial re-evaluation is expected to occur within and among all products of problem formulation.

  - **Analysis** is the technical stage in which exposure and effects are characterized. Analysis of exposure includes the collection of data on source emissions and their

fate and transport that results in exposure to human or environmental receptors. Effects characterization includes the evaluation of toxicity of these emissions and takes into account any criteria that have been established for these substances.

- **Risk characterization** is the phase in which risks are estimated by integrating the estimates of exposure and effects developed in the analysis phase (e.g., stressor-response profiles) and, of equal importance, are presented in the manner most informative to risk managers. This includes a discussion of the assessment's strengths, limitations, assumptions, and major uncertainties.

- The interaction between risk assessors and risk managers is highlighted. The guidelines emphasize the complementary roles of assessors and managers in determining the scope and boundaries of the assessment and selecting endpoints that will be the focus of the assessment. When the risk characterization is complete, the risk assessor must communicate the risks "in a manner that is clear, transparent, reasonable, and consistent" with Agency risk characterizations of similar scope. The interaction between risk assessors and risk managers is critical to ensure that the results of the assessment can be used to support a management decision.

EPA ECOLOGICAL RISK ASSESSMENT GUIDANCE DOCUMENTS

Since 1990, EPA has published several documents (listed below) intended to improve the quality and consistency of Agency ecological risk assessments.

- *Framework for Ecological Risk Assessment* (EPA 1992b)
- *A Review of Ecological Assessment Case Studies from a Risk Assessment Perspective* (EPA 1993a; EPA 1994b)
- *Guidelines for Ecological Risk Assessment* (EPA 1998d)

The ecological risk assessment framework presented in the Guidelines is shown in **Exhibit 5** and explained in more detail in later sections. In refining environmental risk assessment methods for the air toxics program in general, and residual risk analyses specifically, we will be referring to the framework and general approaches contained in the Guidelines, the companion case study document, and future supplements.

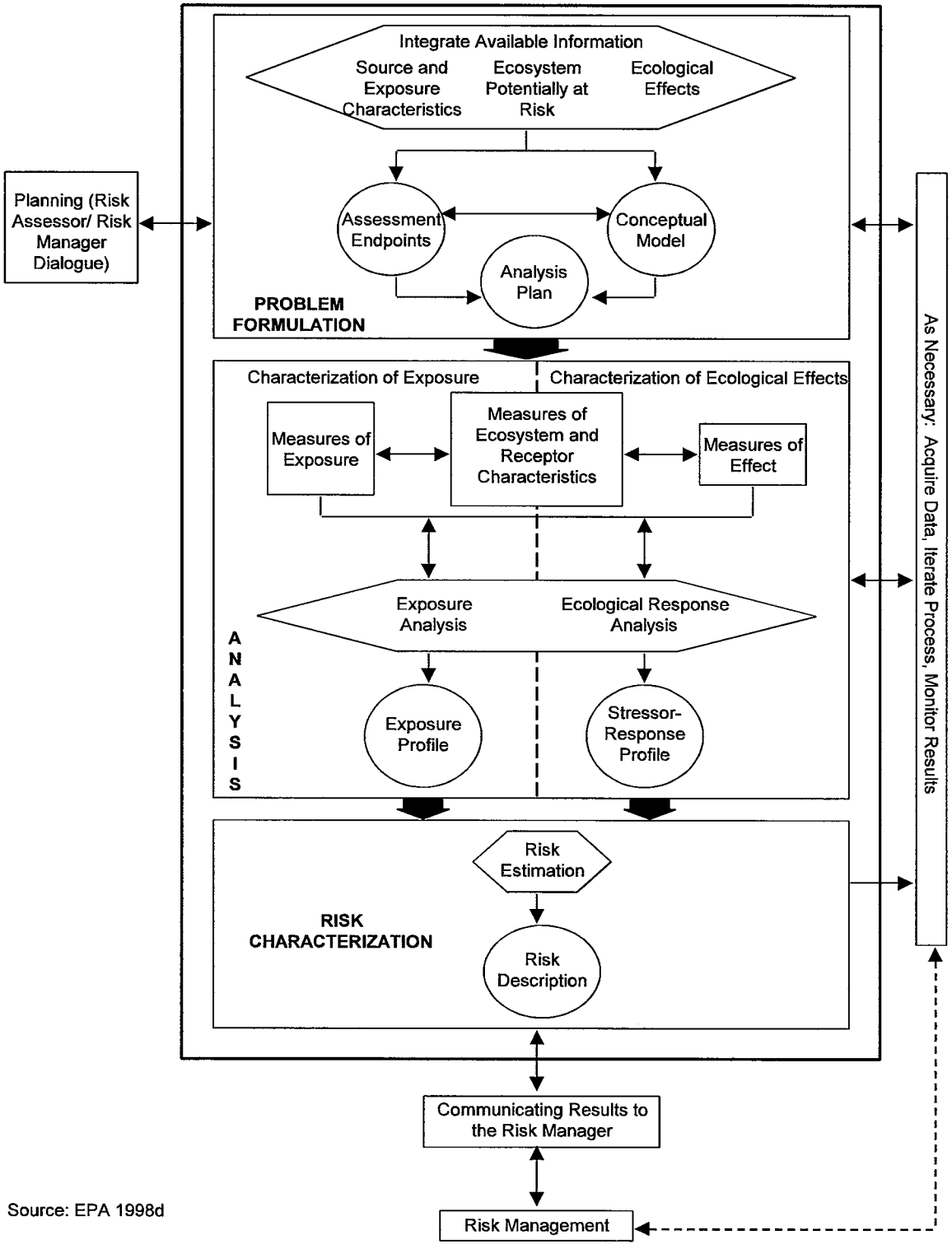
EXAMPLES OF ASSESSMENT ENDPOINTS

- Sustained aquatic community structure, including species composition and relative abundance and trophic structure.
- Sufficient rates of survival, growth, and reproduction to sustain populations of carnivores typical for the area.
- Sustained fishery diversity and abundance.

Source: EPA 1997e

The framework for ecological risk assessment is conceptually similar to the approach used for human health but is distinctive in its emphasis in three areas. First, ecological risk assessment should consider effects beyond those on individuals of a single species, examining effects at a population, community, or ecosystem level. Second, no single set of

EXHIBIT 5
ECOLOGICAL RISK ASSESSMENT FRAMEWORK



Source: EPA 1998d

ecological values to be protected can generally be applied. Rather, these values are selected from a number of possibilities based on both scientific and policy considerations. Given these complexities in the ecological risk assessment process, and its more recent history in EPA guidance, the reader is provided here with a description of some of the unique aspects of the problem formulation stage. The problem formulation stage of ecological risk assessment includes the determination of assessment endpoints, a conceptual model, and an analysis plan.

An assessment endpoint is an explicit expression of the "actual environmental value that is to be protected" or is of concern (EPA 1992b), and includes the identification of the ecological entity for the analysis (e.g., a species, ecological resource, habitat type, or community) and the attribute of that entity that is important to protect and that is potentially at risk (e.g., reproductive success, production per unit area, surface area coverage, or biodiversity) (EPA 1998d). A manageable subset of the most important assessment endpoints is selected for the risk assessment, and the measures by which these endpoints will be assessed are also identified. Additional issues important to the identification of assessment endpoints, which will be considered in ecological risk assessments for air toxics, are provided in the *Guidelines for Ecological Risk Assessment* (EPA 1998d).

Appropriate selection of relevant assessment endpoints is critical in order that the risk assessment provide valuable input to the associated risk management decisions. Assessment endpoints that can be measured directly are most effective, although assessment endpoints that cannot be measured directly, but can be represented by measures that are easily monitored or modeled may also be used. Additional uncertainty is introduced depending on the relationship between the measure and the assessment endpoint. Examples of assessment endpoints, measures of effect, and other elements of the problem formulation phase are presented in the text box for EPA's water quality criteria derivation process.

A second component of the problem formulation phase for ecological risk assessment is the development of a conceptual model to describe potential interactions between pollutant emission and the assessment endpoints. The model includes both the relevant risk hypotheses and a diagram which links pollutant emissions, exposure pathways, ecological receptors, and ecological effects. Risk hypotheses are statements that describe possible relationships between emissions of a pollutant, exposure, and assessment endpoint response. They include the information that sets the problem in perspective as well as an identification of the proposed relationships that need evaluation (EPA 1998d). Consequently, conceptual models developed early in the process are intended to be broad in scope and identify as many potential relationships as possible. As more information is incorporated, we assess the plausibility of specific hypotheses and identify the most appropriate risk hypotheses for subsequent evaluation in the analysis phase of the risk assessment. The following examples, one specific and one generic, illustrate risk hypotheses involving the contribution of air pollutants to aquatic ecosystem risks (EPA 1998d).

- Nutrient loadings from septic systems, air pollution, and lawn fertilizers cause eelgrass loss in Waquoit Bay by shading due to algal growth and direct toxicity from nitrogen.

- When a specific chemical (e.g., a HAP) is released to the environment at a specific rate, based on the chemical's K_{ow}, its mode of action, and the food web of the target ecosystem, it will bioaccumulate sufficiently in "X" years to cause developmental problems in receptors of concern (e.g., fish).

Conceptual model diagrams are used, along with the risk hypotheses, to select the pathways to be evaluated in the analysis phase of the ecological risk assessment, as well as to assist in communication with risk managers. There is no set configuration for conceptual model diagrams. **Exhibit 6** is a conceptual model diagram for exposure of piscivorous birds to HAPs.

In preparation for the analysis step, the data and measures to be used in evaluating the risk hypotheses are identified in an analysis plan (EPA 1996d). That is, we identify the ways we will quantify HAP exposure (e.g., incorporating information such as emission rates, dispersion, persistence and partitioning properties) and effects (e.g., survival, growth, reproduction, and community structure). In the analysis plan we also specify how risks will be characterized.

AN EXAMPLE OF ECOLOGICAL RISK ASSESSMENT PROBLEM FORMULATION: EPA'S WATER QUALITY CRITERIA

A specific example of elements of the problem formulation phase in a national-level ecological risk assessment, as provided in *EPA's Guidelines for Ecological Risk Assessment* (EPA 1998d) can be found in the development of AWQC by EPA's Office of Water under the CWA. Water quality criteria have been developed for the protection of aquatic life from chemical stressors (EPA 1986d). This text box shows how the elements of a water quality criterion correspond to elements of problem formulation, which include management goals, management decisions, assessment endpoints, and measures. These elements of problem formulation support subsequent analyses in the risk assessment.

Regulatory Goal

- CWA, section 101: Protect the chemical, physical, and biological integrity of the Nation's water

Program Management Decisions

- Protect 99% of individuals in 95% of the species in aquatic communities from acute and chronic effects resulting from exposure to a chemical stressor

Assessment Endpoints

- Survival of fish, aquatic invertebrate, and algal species under acute exposure
- Survival, growth, and reproduction of fish, aquatic invertebrate, and algal species under chronic exposure

Measures of Effect

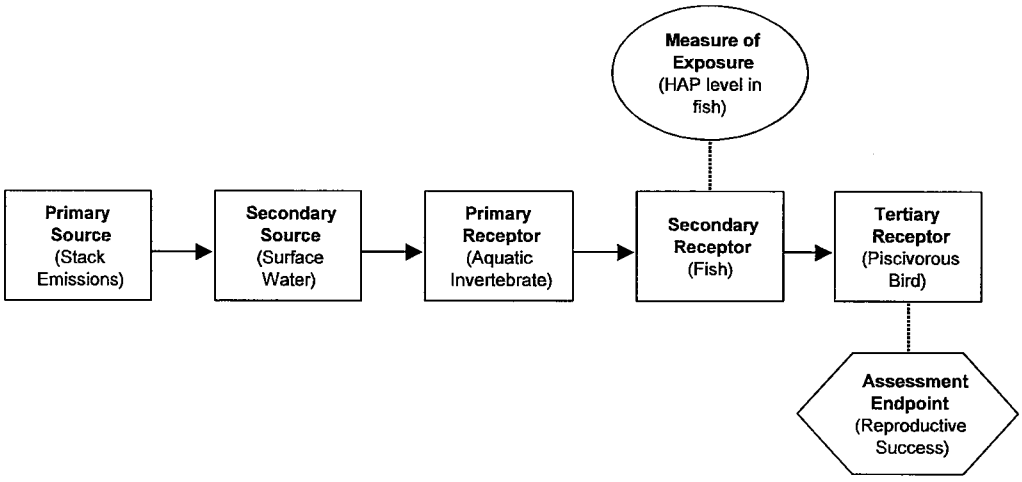
- Laboratory LC_{50}s for at least eight species meeting certain requirements
- Chronic no-observed-adverse-effect levels (NOAELs) for at least three species meeting certain requirements

Measures of Ecosystem and Receptor Characteristics

- Water hardness (for some metals)
- pH

The water quality criterion is a benchmark level derived from a distributional analysis of single-species toxicity data. It is assumed that the species tested adequately represent the composition and sensitivities of species in a natural community (EPA 1986d).

EXHIBIT 6
CONCEPTUAL MODEL DIAGRAM FOR EXPOSURE OF PISCIVOROUS BIRDS TO HAPs



3.2 *Framework for Risk Assessment*

Using knowledge gained from past risk assessments, information from other regulatory agencies, and guidance from Reports such as the NRC and CRARM reports, the Agency has developed a general framework for assessing residual risks. Consistent with the recently published *Guidelines for Ecological Risk Assessment* (EPA 1998d), and noted in Section 3.1.4, each human health and ecological risk assessment is organized into three phases.

- In the **problem formulation** phase, the content and scope of the assessments are specified. This phase includes identifying goals and assessment endpoints, preparing a conceptual model, and developing an analysis plan.

- The **analysis** phase involves evaluating exposure and effects and the relationship between them.

- **Risk characterization** requires estimating and interpreting risk through integration of the exposure and effects analyses. The risk results are presented in context with the uncertainties and limitations of the analysis and other relevant information.

Current thinking regarding both human health and ecological risk assessments recommends reliance on a tiered or iterative approach, beginning with a simple screening analysis and moving as warranted to a more detailed and resource intensive analyses (NRC 1994; CRARM 1997a,b; EPA 1998d). When the available information precludes the need for screening analysis, it may be omitted. Each assessment includes the three phases.

Three of the four components of the risk assessment paradigm introduced by NAS (as described in Section 3.1.1) – exposure assessment, hazard identification, and dose-response assessment – fall within the analysis phase of risk assessment. The fourth component of the NAS paradigm is the risk characterization. In the NAS paradigm, information from the three types of analysis is combined to yield a characterization of risk.

- The level of exposure being received by people from the pollutant source is estimated in the exposure assessment.

- The type and severity of adverse effects that can be caused by the pollutant are assessed in the hazard identification step of the effects assessment.

- The adverse effects of a pollutant observed at different levels of exposure and the relationship between exposure and effects are considered in the dose-response assessment step of the effects assessment.

The presentation in this chapter of both human health and ecological risk assessment methods is organized into three sections, which parallel the three components of the analysis phase: Exposure Assessment in Section 3.3, Effects Assessment (includes both hazard identification and dose-response assessment) in Section 3.4, and Risk Characterization in Section 3.5.

3.3 Exposure Assessment

The nature and complexity of the exposure assessment is often a function of the particular risk management question (or other purpose) to be addressed. Simple screening analyses, using conservative default assumptions, are appropriate to rule out the need for further analyses or action. On the other hand, a detailed exposure analysis may be needed to determine the necessity for or type of emission controls, particularly when those controls are associated with large economic consequences. In some cases, the critical policy question may be to estimate the risks to a small subset of the population at high exposure levels, whereas in another, the overall risks across the entire nation may be the driving policy question. Either human health or ecological risks may be the main focus of a given exposure assessment. Thus, there is no single "right" way to conduct an exposure assessment.

The initial EPA *Guidelines for Exposure Assessment* were issued on September 24, 1986 (EPA 1986f) and the *Proposed Guidelines for Exposure-related Measurements* on December 2,

1988 (EPA 1988a). In response to recommendations from the EPA Science Advisory Board and the public, the 1986 Guidelines were updated and combined with the 1988 Proposed Guidelines and reissued as the 1992 *Guidelines for Exposure Assessment*, which were published in final form on May 29, 1992 (EPA 1992a). Publication of the 1992 Guidelines made information on the principles, concepts, and methods used by the Agency available to all interested members of the public. The Guidelines establish a broad framework for Agency exposure assessments by describing the general concepts of exposure assessment, including definitions and associated measurement units, and by providing broad guidance on the planning and conduct of an exposure assessment. The Guidelines also provide information on presenting the results of the exposure assessment and characterizing uncertainty. Although the Guidelines focus on exposure of humans to chemical substances, much of the guidance also pertains to assessing ecological exposure to chemicals, or to human exposures to biological, radiological, or other agents.

In the Guidelines, EPA established a specific definition of exposure to minimize ambiguity in the use of terms and units for quantifying exposure (EPA 1992a). Human exposure is defined as contact with a chemical or agent at the visible external boundary of a person, including skin and openings into the body such as mouth and nostrils (but not necessarily contact with exchange boundaries where absorption may take place, such as skin, lung, and gastrointestinal tract). Therefore, an exposure assessment is the quantitative or qualitative evaluation of contact, and includes such characteristics as intensity, frequency, and duration of contact. Often, an assessment also will evaluate the rate and route at which a chemical crosses the external boundary (dose) and the amount absorbed (internal dose). The numerical output of an exposure assessment may be either exposure or dose, depending on the purpose of the evaluation.

Exposure characterization for ecological risk assessment describes potential or actual contact or co-occurrence of air toxics concentrations with ecological receptors. It is based on measures of exposure and ecosystem and receptor characteristics that are used to analyze HAP sources, their distribution in the environment, and the extent and pattern of contact or co-occurrence. The objective is to produce a summary exposure profile that identifies the exposed ecological entity, describes the course a stressor takes from the source to that entity (i.e., the exposure pathway), and describes the intensity and spatial and temporal extent of co-occurrence or contact. The profile also describes the impact of variability and uncertainty on exposure estimates and reaches a conclusion about the likelihood that exposure will occur (EPA 1998d).

An exposure assessment has four major components: emissions characterization, environmental fate and transport characterization, characterization of the study population, and exposure characterization. These components are discussed individually in this section.

3.3.1 Emissions (Source) Characterization

In the first step of exposure assessment for air toxics, the specific HAPs emitted and the sources of their airborne emissions are determined. Data are collected on the emission rates of the pollutants and parameters of the source. Knowledge of the emission rate and release characteristics enables the pollutant fate and transport to be estimated.

Ideally, the emission estimates are from direct measurements of source emissions. Although direct measurement is likely to provide the most accurate data for an emission source, these data are typically not available, as such sampling is often time- and resource-intensive. When specific emission measurements are not feasible or available, other emission estimation methods, including material balances and emission factors, are sometimes used as an alternate method. Emission factors indicate the quantity of a pollutant typically released to the atmosphere for a particular source operation, and are usually considered to be representative of an industry or emission type as a whole. Actual emissions from a specific source may be higher or lower or may be comprised of a different set of individual HAPs than the emission factors indicate because of site-specific process design, control equipment, operation and maintenance practices, or other factors. Before using an emission factor, available documentation on how the emission factor was derived should be studied to determine whether it is appropriate for the source under consideration. Each approach to estimating emissions, including use of direct measurement data, has an inherent level of uncertainty, which adds to the overall uncertainty of a risk analysis.

HAPs THAT ARE GROUPS OF CHEMICALS

As described later in Exhibit 19, there are 17 HAPs that represent groups of chemicals rather than individual compounds, substantially complicating the exposure assessment process. In the case of the 12 elements listed (e.g., mercury compounds), obtaining emissions information may be complicated by speciation of the element as well as its combination with other chemicals. As another example, the HAP polycyclic organic matter (POM) is a complex mixture of thousands of polycyclic aromatic compounds. In order to obtain consistent emission estimates for such a complex chemical group, the Agency has identified three representative subgroups for which emissions inventories are usually compiled: (1) 7-PAH includes the seven polynuclear aromatic hydrocarbons that we have identified as probable human carcinogens; (2) 16-PAH includes the 7-PAH group plus nine other commonly measured PAHs; and (3) EOM (extractable organic matter) is the extractable subfraction of particulate matter that some research indicates may provide a better estimate of POM cancer risk than any of the individual PAHs or PAH subgroups.

Source parameters define how the pollutant is released to the environment, and they affect the initial dispersion of the pollutant in the atmosphere. For point sources of air toxics, source parameters can include the volume flow rate or exit velocity of the stack gas, stack gas exit temperature, stack height, inner stack diameter, knowledge of the proximity of structures to the release point, and other characteristics. For small sources within a larger facility (e.g., emissions from storage piles or ponds), the dimensions of the small source should be identified. While point source emission rates are expressed in terms of mass per unit time, non-point source emission rates are more typically modeled in terms of mass per unit time per unit area. Another important consideration in specifying the source emission rates is whether the rates should reflect short-term or annual operating conditions. Ideally, it is better to have hourly or daily emission

rates; however, these data are not typically available. Short-term emission rates provide the flexibility to model emissions over a range of release times, to assess risk over shorter intervals than annual, and to permit more accurate assessments through the incorporation of microenvironment and population activity pattern analyses.

Depending on the analysis, source and emissions data can be derived from broad-scale emission inventories, specific data collection efforts with particular industries, or information from regional, State, or local air toxics agencies. Other information, such as the geographic location of release points, the temporal pattern of emissions (e.g., periodic "puffs" vs. constant emission rates), and the release height may be necessary depending on the level of detail needed or types of exposure examined in the assessment.

Data and Tool Availability, Limitations, and Closing Gaps

In the analyses to be performed under the residual risk program, it is important that the data, regardless of the form in which they are obtained, represent post-MACT emissions (i.e., estimated or measured HAP emissions for a source that has already implemented MACT standards). In collecting the variety of information for each source category (e.g., emissions, source characteristics), there are several data sources we will be consulting:

- EPA's National Toxics Inventory (NTI) (see text box below);
- State or local air toxics agencies;
- Industry;
- EPA's Aerometric Information Retrieval System (AIRS);
- EPA's Toxic Release Inventory (TRI); and
- MACT development data.

While the 1996 and future generations of the NTI are intended to contain facility-specific data and to support site-specific modeling applications, the timing for completion of the 1996 version precludes its use for the initial residual risk analyses. For these analyses, data will be obtained from the same sources (see preceding list) that are being consulted in development of the 1996 NTI. The hierarchy of preference for source data for assessments will be consistent with that established to ensure the rigor of the NTI. For source categories for which the MACT compliance date has not yet occurred, however, a screening risk assessment may be performed based on information compiled by EPA during the MACT rule development process for that source category. Refined analyses will typically rely on the availability of post-MACT emissions data.

3.3.2 Environmental Fate and Transport Characterization

After the pollutants of interest and their sources and emission rates are defined, the exposure assessment process continues with estimation of pollutant fate and transport. This step describes how the pollutant is transported, dispersed, and transformed over the area of interest.

THE NATIONAL TOXICS INVENTORY

In 1995, EPA initiated development of the National Toxics Inventory (NTI), a central repository of air toxics emissions and inventory data for HAPs. Although its development was not explicitly required by the CAA, the NTI is useful in assisting stakeholders in conducting the analyses required by the Act. The NTI is updated every three years, on the same schedule as the criteria air pollutant inventories.

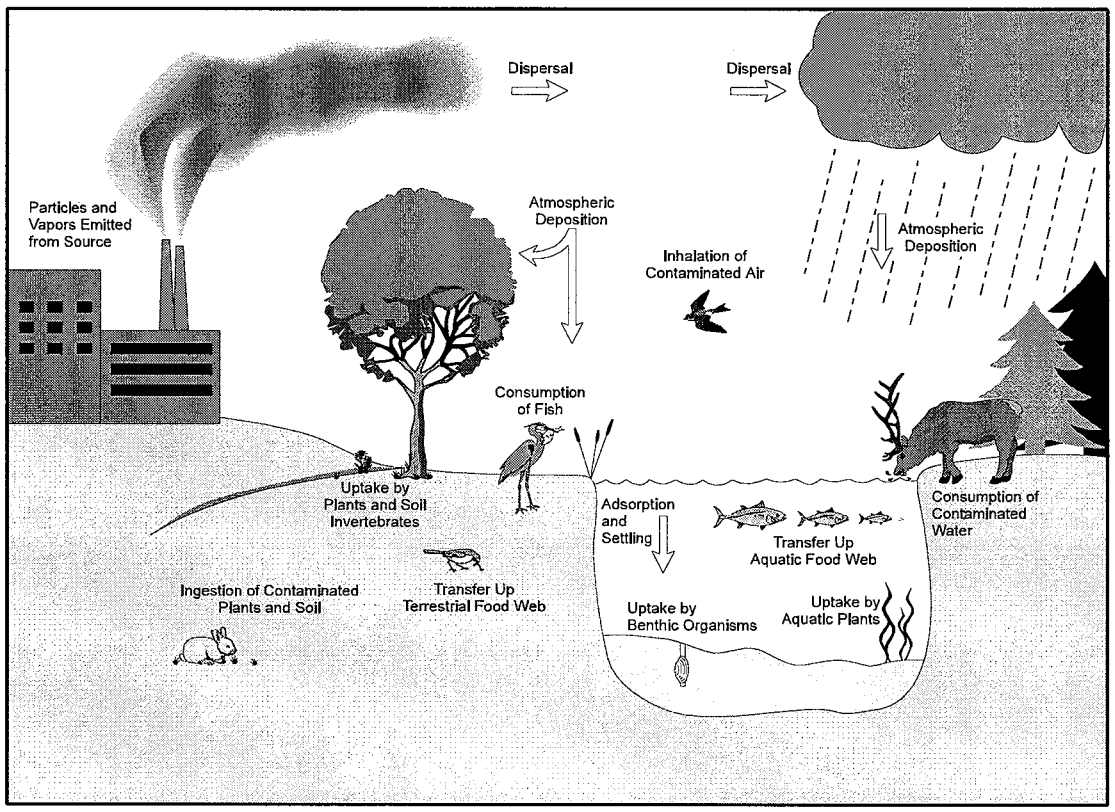
The goal of the NTI is to compile the best available emissions information about the 188 HAPs for many of approximately 960 source categories. The data are from multiple data sources, which we have prioritized to provide the most complete, consistent data repository. The hierarchy of data sources is: (1) data developed by State and local air agencies; (2) data we collected and developed as part of the MACT development process; (3) data from inventories developed to support requirements of section 112(c)(6) and 112(k); (4) emissions reported in the TRI; and (5) emissions generated by the Agency using widely recognized emission factors and activity factors. We have recently compiled the NTI for 1993 and are currently compiling the 1996 inventory, which following review by States is scheduled for completion in October 1999. (For more information on the NTI, see EPA's 1997 Trends Report (EPA 1999).)

Initially, the fate of the emitted pollutants is largely determined by the source release characteristics. After pollutants are released to the atmosphere, their transport, dispersion, and transformation are governed by meteorological principles, terrain characteristics, wet and dry deposition rates, and certain chemical properties of the HAP (such as aqueous solubility, vapor pressure, air-water partition coefficient (i.e., Henry's Law constant), molecular diffusivity, phase partition coefficient, melting point, and adsorptivity). For a limited subset of HAPs, it is important to consider deposition from air to soil, vegetation, or waterbodies. For others, such deposition is not important.

A variety of mathematical models, each with specific data needs, has been developed or is under development to describe the transport and fate of pollutants released to the atmosphere. The model chosen must be appropriate for the intended application, which may vary among estimates of short-term peak concentrations immediately adjacent to a facility, long-term concentrations over a city-wide area, or deposition over hundreds or even thousands of miles. The HAP's reactivity and persistence will influence its fate as well and can be important factors in estimating exposure for certain pollutants. Additionally, secondary transformation products of some HAPs may need to be identified for consideration in risk assessment. High quality, representative meteorological information is crucial to a valid exposure assessment for air toxics, as well as information on local topography. Any available HAP monitoring data can be used either to check the validity of modeled concentration estimates or as a primary or supplemental source of information for the exposure assessment itself.

Many studies indicate that a limited number of pollutants emitted into the atmosphere (e.g., mercury) are passed to humans or wildlife through non-inhalation pathways (EPA 1990). An example would be a HAP depositing from the air onto the soil, followed by ingestion of the soil by a child or by biota in an ecosystem. **Exhibit 7** is an example of the conceptual model diagram for an ecological risk scenario involving multipathway exposure to HAPs. For a limited subset of HAPs, greater human and ecological exposures to the HAP occur through non-

EXHIBIT 7
CONCEPTUAL MODEL DIAGRAM FOR MULTIPATHWAY EXPOSURE TO AIR TOXICS



inhalation exposures than through inhalation exposures. These HAPs typically are persistent in the environment, have a strong tendency to bioaccumulate, and exhibit moderate to high toxicity.

Data and Tool Availability, Limitations, and Closing Gaps

Modeling. The Agency relies on a variety of models for air dispersion modeling. Tier 1 from *A Tiered Modeling Approach for Assessing the Risks Due to Sources of Hazardous Air Pollutants* (EPA 1992c), SCREEN3 (EPA 1995b), and others (NRC 1994) are available for simpler types of applications and needs. As the applications and needs become more complex, the Industrial Source Complex Short-Term 3 model (ISCST3), a Gaussian plume model, can be used to estimate both short-term peak and long-term average air concentrations and deposition rates (EPA 1995c). In addition, the Agency is working with the scientific community to develop improved dispersion models such as AERMOD (EPA 1998e).

Regardless of the model used in the exposure assessment, it is important to ensure that the averaging time of exposure estimates derived from a modeling exercise are appropriate for the time frame of interest (e.g., short-term acute exposure or long-term chronic exposure). Dispersion models such as ISCST3 are designed to estimate ambient pollutant concentrations on the order of an hour or to run multiple hourly iterations to calculate longer-term averages such as seasonal or annual average concentrations. It should be noted, however, that ISCST3 is designed to calculate ambient pollutant concentrations resulting from an emission source that has an essentially constant release rate over an extended period of time (e.g., over a month or year). Therefore, ambient concentrations that result from intermittent emissions (such as those resulting from an industrial batch process) may not be predicted accurately by this model. Other EPA models can predict short-term concentrations from pulse or intermittent releases. It is also important to note that the type and quality of input data available to the model can affect the accuracy and usefulness of the modeling results (e.g., whether available meteorological data are representative of site conditions, whether emissions estimates are available on an annual or monthly basis, whether the site is in simple or complex terrain).

Various equations and scenarios are available for modeling exposures that occur through routes other than inhalation, and each equation requires the appropriate input data. The simplest multipathway exposure assessments require chemical-specific data (e.g., octanol-water partition coefficient (K_{ow})) to model the partitioning of the chemical in the environment and uptake rates (e.g., 3 liters water/day) to predict intakes. Combining this information yields general predictions of non-inhalation exposure.

The EPA's initial detailed guidance on multipathway exposure assessment methods was issued by ORD in 1990 (EPA 1990), updated a few years later (EPA 1993b), and recently consolidated and updated again (EPA 1997f) . These documents present the Indirect Exposure Model (IEM), which consists of equations and default input values to be used in calculating exposure levels for a set of multimedia, multipathway exposures. The associated equations for such an analysis typically start with atmospheric deposition rates and require additional chemical data and many other input parameters related to the environmental setting and population. For example, modeling pollutant fate and transport through a waterbody requires information such as waterbody location, size, and drainage area for each waterbody being evaluated. As another example, modeling exposure via vegetable consumption involves parameters such as soil type, soil depth, annual rainfall, and vegetable type (e.g., root, leafy). A critical input to these calculations for the location(s) being assessed is the HAP deposition rate (i.e., amount per unit time being deposited from the air to land and/or surface water), which can be estimated using air models such as EPA's ISCST3. The Total Risk Integrated Methodology (TRIM) model, a new multimedia, multipathway exposure model under development by EPA is discussed in a later section.

Monitoring Data. With the exception of monitoring for a limited number of volatile organic HAPs, there is no national ambient air quality monitoring network making routine measurements of air toxics levels. Therefore, ambient data for individual HAPs are limited (both

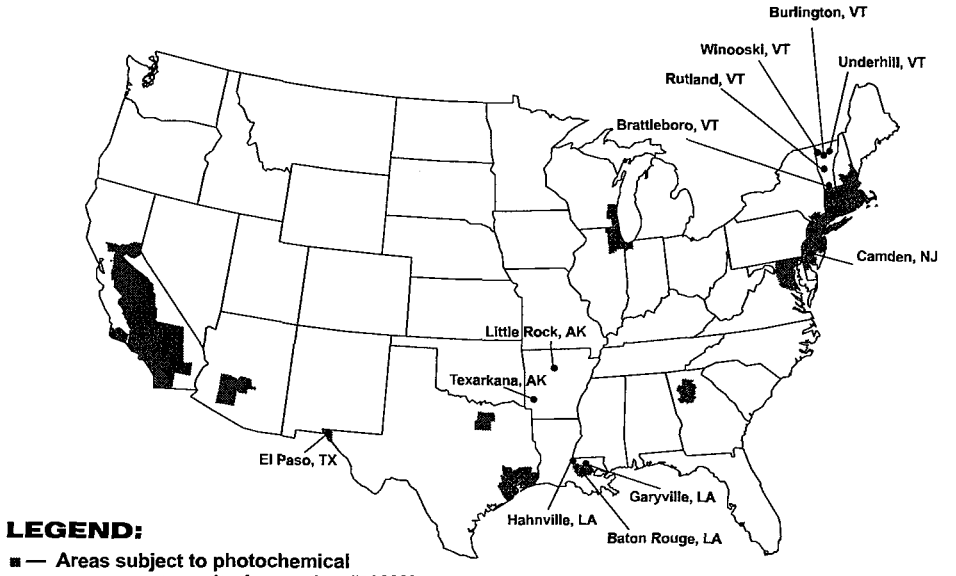
spatially and temporally) in comparison to the data available from the long-term, nationwide monitoring for the six criteria air pollutants. However, several State and local agencies operate independent toxics monitoring programs. For example, the California Air Resources Board has administered a 30-site Toxics Data Network since 1985, and the Texas Natural Resources Conservation Commission initiated a 22-site Community Air Toxics Monitoring Network in 1992. In addition, EPA sponsors the Urban Air Toxics Monitoring Program (UATMP), a "participatory" or voluntary program through which State and local agencies can take part in air toxics monitoring. The UATMP involves measurements of 38 volatile organic compounds and 16 carbonyl compounds; in 1997, the UATMP was comprised of 12 monitoring stations in five States (see **Exhibit 8**).

Although designed primarily as an effort to monitor and characterize ozone precursors, the Photochemical Assessment Monitoring Stations (PAMS) program also includes measurement of several HAPs: acetaldehyde, benzene, ethyl benzene, formaldehyde, hexane, styrene, toluene, 2,2,4-trimethylpentane, and xylenes (m,p,o-xylene). Initiated in February 1993, the PAMS program requires establishment of an enhanced monitoring network in all ozone nonattainment areas classified as serious, severe, or extreme. The 24 affected areas, shown in Exhibit 8, cover approximately 120 thousand square miles and have a total population of 84 million people (approximately 30 percent of the U.S. population). The PAMS program may play a significant role as a foundation for future ambient monitoring for air toxics. Additionally, ambient air quality data for some HAP constituents of particulate matter (e.g., some elements and semi-volatile organic compounds) may be obtained under the current plans for the national $PM_{2.5}$ (fine particulate matter) speciation network.

Without a national mandate for ambient monitoring for air toxics, there is also little incentive for the data from these various programs to be centrally archived. The Agency is attempting to remedy this problem through an ongoing effort to identify all sources of ambient air quality data for toxics. The newly identified data are being compiled into a data base, which is updated on a quarterly basis. Recognizing competing resource needs, EPA is encouraging State and local agencies to tailor their monitoring programs to address their most pressing air toxics issues and local needs. EPA is also requesting that the State and local agencies work with EPA to develop a monitoring network distribution that capitalizes on existing efforts and capabilities. EPA expects to add 17 new monitoring sites to this network in 1999. This will include one new site in the major metropolitan areas of each of the 10 EPA Regions and an additional site in each of the seven areas with existing PAMS networks. EPA expects to increase that number by up to 40 additional sites in 2000.

It should be noted, however, that for the purposes of risk assessments, specifically residual risk assessments, even comprehensive and high quality monitoring data would not be adequate and would need to be supplemented with modeling data. For example, the contributions of individual sources and source categories often cannot be determined based on monitoring data alone.

EXHIBIT 8
URBAN AIR TOXICS MONITORING PROGRAM SITES (1997)
AND PHOTOCHEMICAL ASSESSMENT MONITORING STATIONS OR PAMS (1998)



While not collected specifically for air toxics assessment purposes, monitoring data for non-air media (e.g., soil, sediments, surface water, biota) are collected under programs sponsored by EPA and other federal agencies and by the States. A number of these programs collect data on sets of pollutants that overlap with the 188 HAPs. For example, the Agency's Environmental Monitoring and Assessment Program (EMAP) monitors polycyclic aromatic hydrocarbon (PAH), polychlorinated biphenyl (PCB), DDT, other pesticide, and butyltin levels in sediments in three large estuarine areas (Mid-Atlantic, Gulf of Mexico, and Louisiana). Under the National Status and Trends programs implemented by the National Oceanic and Atmospheric Administration, chemical contaminant levels are monitored in fish and surficial sediments from 170 coastal and estuarine sites, and chemical contaminant trends in mollusks are tracked at 287 coastal and estuarine sites. Fish, shellfish, and sediment monitoring is also conducted by many States. In addition, air deposition of a small subset of HAPs is measured in selected regions of the country under the CAA Great Waters program. Any of these data sources may be consulted as appropriate for verification of multimedia modeling output or identification of background contaminant levels.

3.3.3 Characterization of the Study Population

After ambient concentrations have been derived, human and/or ecological exposures to these concentrations are determined. In this component, the study population is defined in terms of geographic distribution and other characteristics relevant to the exposure pathways of concern.

For the more frequently performed human inhalation exposure analyses, the locations of resources, homes, workplaces, schools, and other receptor points will partially determine the extent of actual exposure. Factors such as age, sex, and activity patterns affect the amount of pollutant actually inhaled by an individual, while mobility of the subject affects the concentration levels to which an individual is exposed over time. In screening analyses, potential exposure may be estimated using the maximum off-site concentration, which may be more easily calculated than an exposure estimate linked to population location and behavior. In a refined assessment, we will incorporate more specific information about actual receptor points and the population's movement throughout the area, including, if appropriate, the amount of time spent in specific microenvironments (e.g., indoors at home, outdoors, in motor vehicles). Depending on the focus of the analysis, output of the exposure assessment may vary. In some cases the most highly exposed 5 to 10 percent of the population may need to be well-characterized, while for others, the distribution of exposures across a wider area is needed. Information on specific sensitive populations, such as children or the elderly, is another layer of detail that may often be needed in refined analyses.

As with inhalation, assessing non-inhalation exposure to human populations involves combining pollutant concentration information with relevant information concerning the study population. The kinds of information needed depend on the relevant exposure pathways. EPA's Office of Solid Waste and Emergency Response has considered multipathway exposures in various risk assessment activities, including the assessment of hazardous waste combustion (EPA 1994c; EPA 1998f). Examples of recommended pathways include:

Air —deposition→ Soil —ingestion→ Human

Air —deposition + uptake of vapor phase→ Above-ground Vegetable —ingestion→ Human

Air —(see above)→ Soil + Above-ground Vegetable —ingestion→ Beef —ingestion→ Human

Air —(see above)→ Soil + Above-ground Vegetable —ingestion→ Milk —ingestion→ Human

Air —deposition + runoff + erosion→ Waterbody —bioaccumulation→ Fish —ingestion→ Human

Air —deposition→ Surface Water —ingestion→ Human

Air —deposition→ Soil —overland flow→ Surface Water —ingestion→ Human

After identification of the relevant exposure pathways, information such as soil, drinking water, and food ingestion rates (often including specific foods, such as fish, beef, pork, eggs, root vegetables, grains, fruit), generally for both adults and children, as well as contact frequencies with soil and surface water, may be needed. Some activities of particular interest for non-inhalation modeling are subsistence farming and subsistence fishing because of the unique dietary habits of these two groups (i.e., eating much more garden vegetables and fish,

respectively). Also, as with inhalation exposure, the extent to which these factors are included in the risk assessment depends on the purpose of the assessment, available resources, uncertainties in the assessment, and data quality and quantity. Not only are the data requirements often extensive, particularly when many different pathways are being assessed, but the computational demands also can be quite large in a multimedia, multipathway assessment.

To relate estimated ambient concentrations to exposures in ecological assessments, characteristics of the ecosystem and ecological population are identified. These include behavior, location, and important life history characteristics that may affect the exposure or response of assessment endpoints to the HAPs. Examples include the timing of the study population's reproductive cycles or migration patterns in relation to ambient concentrations, as well as features of ecosystem habitats which may affect exposures. A screening-level multipathway assessment may be used to identify potentially significant exposure pathways and to develop an exposure profile for ecological receptors of concern.

Data and Tool Availability, Limitations, and Closing Gaps

Human Population Assessment. Exposure and risk to human populations via the inhalation route involves combining pollutant concentration information with information on the geographical distribution of people in the study area, including consideration of data on the activities and characteristics of the exposed population. Human exposure and susceptibility and sensitivity to pollutant effects may vary with factors such as age, gender, intensity and amount of activity, time spent in microenvironments, diet, overall health, lifestyle, genetic factors, and the concentration of pollutant. The extent to which these factors are included in the risk assessment depends on the purpose of the assessment as defined in the problem formulation step, available resources, uncertainties in the assessment, and data quality and quantity.

In characterizing the exposed population, the U.S. Bureau of Census is a major source of population information (i.e., the 1990 Census). In air toxics exposure assessment, the Agency typically uses population and demographic data that are based on the census block level. There are approximately 6.9 million census blocks in the U.S. The number of people residing in each census block and the geographical center of each are specifically used in the assessments. The population included within a census block is highly variable (from less than 10 to a few thousand), but, on average, about 30 to 40 people reside in each block. These data provide a good estimate of how people are geographically distributed near emitting sources, and are also useful for defining the population cohorts for analysis. Cohorts may be defined on the basis of age, gender, race, income levels, length of time in primary residence, or other characteristics. Data on population characteristics relevant to exposure potential are obtained from documents and studies such as EPA's *Exposure Factors Handbook* (EFH) (EPA 1997g) and national population surveys of people's activity patterns, including where they spend each hour of a day (microenvironment) and each hour's activity level (EPA 1994d).

In estimating inhalation exposure from stationary sources of HAPs for residual risk analyses, we currently use modeling techniques such as the Human Exposure Model (HEM)

(EPA 1986g). In residual risk analyses, we will be relying on an approach that incorporates more sophisticated techniques using detailed and site-specific information when warranted. Some of these techniques are currently being developed by EPA, e.g., TRIM (described below). In the interim, HEM, which contains meteorological data, census data, an EPA air dispersion model, and to address population activities and the variability associated with exposure assessment, an add-on Monte Carlo simulation routine, will continue to be used in air toxics risk assessments.

Predictions of ambient concentrations and atmospheric deposition derived from atmospheric dispersion models have rarely been validated. Model validation is a difficult, resource intensive process that relies heavily on monitoring data, and often, models predict concentrations that are below the levels that can be detected using current analytic methods. Nevertheless, we continue to seek to improve our modeling techniques by enhancing their capacity to incorporate exposure assessment tools and exposure data bases. For example, over the past decade the Agency has significantly expanded available data bases on human activity patterns (e.g., recent development of the Combined Human Activity Database (CHAD)), breathing rates, residential occupancy periods, and microenvironmental exposures. The outputs of these improvements along with improvements in dispersion models can be used as inputs to HEM, along with more detailed and realistic exposure profiles, to generate better estimates of individual and population risk.

As discussed in Section 3.3.2, the primary tool currently used by the Agency for multipathway exposure modeling of the subset of HAPs for which this is appropriate is the IEM. This model includes a fate and transport component that estimates multimedia concentrations and a component that estimates multipathway exposures. The recently released draft guidance document on hazardous waste combustion risk assessment for human health risks (EPA 1998f) includes a full discussion of multimedia exposures and assessment of the resulting risks. This document will be considered in refining our human multipathway exposure assessment methodology.

Additionally, the Agency is currently developing the TRIM, which is a multimedia, multipathway modeling system being designed to address all quantitative dimensions of a complete residual risk evaluation, including the exposure assessment. The TRIM will provide a framework for assessing human health and ecological risks from exposure to hazardous and criteria air pollutants. It will allow for the evaluation of multipathway exposure to air pollutants, using a dynamic mass-balance approach to estimate the exposure and dose profiles received by selected receptors. Both uncertainty and variability will be explicitly treated within the model framework. The TRIM will consist of four modules: (1) the Environmental Fate, Transport, and Exposure module (TRIM.FaTE), (2) the TRIM exposure event module (TRIM.Expo), which will track population cohorts through time and space, (3) a dosimetry module to account for pollutant uptake, biokinetics, and dose-response in humans, and (4) a risk characterization module. The first module was reviewed initially by EPA's SAB in May 1998, and comments received are

being addressed through further development and testing efforts. The first, second, and fourth modules are scheduled to be reviewed by the SAB in 1999. These three modules should be available for EPA use in the year 2000.

Ecological Exposure Assessment. Emission sources, HAP distribution in the environment, and contact with ecological receptors are described in the ecological exposure characterization. Much of the information used in this characterization is similar to that used for the human exposure assessment. For example, monitoring data and emissions and multipathway modeling are major sources of information. As with human exposure assessment, non-inhalation pathways may be important for a limited subset of HAPs that are persistent and/or have the potential for bioconcentration and biomagnification in aquatic and terrestrial food webs. This potential is evaluated based on fate and transport data specific to the pollutant of concern, such as the K_{ow}, organic carbon-water partition coefficient (K_{oc}), and bioconcentration factor (BCF) or bioaccumulation factor (BAF) values.

Some of the information needed to characterize the contact of a pollutant such as a HAP with potential receptors, however, is specific to the ecological risk assessment methodology. For example, an understanding of the site characteristics, including such factors as site topography, soil and water types, and habitat types, is important. Furthermore, the "significance" of potential ecological effects depends on other site-related factors, including the type and significance of the ecological receptors affected and the areal extent of exposures at concentrations sufficient to cause adverse effects. Tools risk assessors can use to determine the locations and types of ecological receptors in areas surrounding the sources include information gathered using maps (e.g., U.S. Geological Survey, National Wetlands Inventory, and EPA's ESTAT Geographical Information System), aerial photographs, communication with scientists knowledgeable about the area (e.g., State agencies, U.S. Fish and Wildlife Service, National Oceanic and Atmospheric Administration), and site surveys.

In the absence of readily available site-specific information and prior to the recommendation of a site-specific ecological risk assessment, it may be appropriate to use approximate source location information to infer the existence of adjacent aquatic and terrestrial ecosystems, and a set of assessment endpoints can be selected that represent the most appropriate sensitive elements of those ecosystems for the contaminants in question. The Agency is considering these issues in developing an approach for use in residual risk ecological exposure assessment activities.

3.3.4 Exposure Characterization

In the exposure characterization component, the pollutant concentration and study population are spatially integrated to characterize exposure (EPA 1993c). For a human health inhalation risk assessment, predicted ambient air concentrations for a certain location – for example, the location of the individual most exposed (see text box) – are compared to the population at that point, taking into account factors that can affect the population's exposure as

MIR, MEI, AND INDIVIDUAL MOST EXPOSED

Maximum individual risk (MIR) is a concept included in the benzene NESHAP and is similar but not identical to the concept of maximum exposed individual (MEI) risk. An MIR represents the highest estimated risk to an exposed individual in areas that people are believed to occupy. The MEI risk represents the highest estimated risk to a hypothetical exposed individual, regardless of whether people are expected to occupy that area. Thus, MEI risk is greater than or equal to MIR.

Depending on the expected magnitude of risk and ready availability of appropriate data, we may use the maximum modeled off-site concentration in screening-level risk assessments. Where risks are expected to be elevated, in order to conserve resources, we may pass over this conservative assumption step and incorporate population data to derive the MIR for areas that people are believed to occupy.

We are proposing that the "individual most exposed," a phrase used in CAA section 112(f)(2), be considered equivalent to the MIR for areas that people are believed to occupy for the purposes of regulation under the residual risk program.

described above. If non-inhalation (multimedia) exposures are of concern, these pathways and the potentially affected populations are considered as well.

The exposure characterization of an ecological risk assessment describes the sources of HAPs, the distribution of HAPs in the environment, and the contact of HAPs with ecological receptors. The characterization is based on measures of exposure and of ecosystem and receptor characteristics developed initially in the problem formulation phase. Many aspects of the exposure characterization process, especially analyzing the sources and distribution of HAPs in the environment, are similar for the ecological and the human health exposure assessment. The primary difference is that the exposure points for ecological receptors can differ from those for humans. Moreover, for ecosystems, exposure "areas" may be more meaningful than exposure "points."

In recent years, there has been increasing interest in explicitly characterizing the extent of uncertainty and variability in risk assessment, and especially in the exposure assessment step. To do this, we may use various approaches, including a technique known as Monte Carlo simulation analysis. Using this technique, important variables in the exposure assessment (as well as in the other parts of the risk assessment) are specified as distributions (rather than as single values) according to what can be expressed about their underlying variability and/or uncertainty. Variables are sampled repeatedly from these distributions and combined in the analysis to provide a range of outcomes. While this technique can offer a useful summary of complex information, it must be noted that the analysis is only as good as the underlying data. It is important that the individual modeled variables are expressed in a way consistent with the best information available, or the results of the Monte Carlo analysis can do more to confuse than enlighten.

3.4 Effects Assessment

3.4.1 Human Health Effects

Hazard Identification

An initial step in the effects assessment is to determine whether the pollutants of concern are causally linked to adverse health effects. This is the hazard identification. Factors such as the route of exposure, the type and quality of the effects, the biological plausibility of findings, the consistency of findings across studies, and the potential for bioaccumulation all contribute to the strength of the hazard identification statement. There are many sources of information that can be brought to bear in the hazard identification. **Exhibit 9** summarizes important sources of information for hazard identification.

HAZARD IDENTIFICATION FOR MIXTURES

While some groups of pollutants, when part of a multiple chemical exposure, act independently in causing health effects, others may interact and elicit an effect that may be different or may occur at a different exposure level than would be expected if exposure were to the chemicals individually. Even when individual pollutant levels are so low that exposure to them one at a time would not be expected to pose harm, some mixtures of pollutants may work together such that their potential for harm adds up and exposure to the mixture poses risk. For some groups of pollutants that can interact chemically, the total risk they pose as a group is greater than what would be expected from adding up the individual risk posed by each. This is known as a synergistic relationship. Antagonistic relationships between chemicals are also possible. In this case, the pollutants interfere with one another and the potential for harm is lessened. This is a significant simplification, but the important point to note is that depending on the mixture of pollutants, the total effect may be different than what would be expected from separate exposures to the individual pollutants because of the potential for additive, synergistic, or antagonistic relationships among some chemicals.

The types of effects that are relevant to a particular chemical (e.g., cancer, non-cancer) are determined as part of the hazard identification. The current approaches for dose-response assessment and risk characterization can differ for various types of effect.

Non-cancer Effects – Chronic and Acute. In large part due to the wide variety of endpoints, hazard identification procedures for non-cancer effects are less formally described in EPA guidance than procedures for the identification of carcinogens. The EPA has published guidelines for assessing several specific types of non-cancer effects, including mutagenicity assessment (EPA 1986a), developmental toxicity assessment (EPA 1991), neurotoxicity assessment (EPA 1998c), and reproductive toxicity assessment (EPA 1996c). Rather than specifying risk assessment methodology, these non-cancer guidelines tend to focus on the proper conduct of testing and the appropriate toxicological interpretation of results of the commonly performed assays. The guidance for hazard identification decisions is fairly general.

For assessment of chronic toxic effects other than cancer, EPA's general approach to hazard identification is to review the health effects literature and characterize its strengths and weaknesses, using primarily a narrative approach rather than a formal classification scheme. Available data on different endpoints are arrayed and discussed, and the effects (and their

EXHIBIT 9
SOURCES OF INFORMATION FOR HAZARD IDENTIFICATION

- **Epidemiologic Data.** Epidemiologic studies of human populations exposed to HAPs in occupational settings or in the general environment can provide valuable information on the effects of HAPs. These studies have advantages over other sources of information in that they directly assess the effects of exposure to humans and, in the case of studies of the general population, address exposures that actually occur in the environment. In addition, recent work with biomarkers (chemicals in the body which allow for better quantification of exposure) promises to boost the utility of epidemiology in the future. Shortcomings include concerns about the relevance of high exposure levels often seen in occupational studies to environmental concentrations, concerns over the control of confounding variables (such as tobacco use) that may obscure true causal relationships (or imply false ones), difficulties in adequately characterizing exposure, and the difficulty most epidemiologic studies have in discerning subtle effects (see Section 4.2.1 for a more complete discussion of epidemiologic data in the context of section 112(f)).

- **Human Data from Case Reports or Controlled Exposure Studies.** Where available, human health effects data from case reports or controlled exposure studies can be extremely valuable, although such data generally have shortcomings. Case reports often involve one or a small number of people, limiting the ability to generalize from them, and they may involve exposures very different than typical environmental exposures. For most HAPs and effect types of interest, controlled human exposure studies are unlikely to be available.

- **Animal Toxicology Data.** High quality studies of human populations exposed to HAPs are rare, due to both expense and the inherent limitations of epidemiology. As a result, EPA and others commonly rely on animal studies to infer potential risk to humans. Animal toxicologic data are typically much easier to obtain than good epidemiologic data, and effects can be explicitly linked with exposure to the HAP(s) being tested with little fear of confounding. However, issues of high-to-low dose relevance are compounded by the need to extrapolate the effects seen in animals to those anticipated in humans. Although there have been considerable advances in understanding the relevance of specific results in animal studies to human biology, such extrapolations remain a considerable source of uncertainty. The EPA has operated under the conservative public health policy that assumes that adverse effects seen in animal studies indicate potential effects in humans.

- **Short-term *in Vitro* Assays.** *In vitro* tests can be carried out quickly and at relatively low cost, and they can provide valuable information on specific aspects of a pollutant's toxicity, such as a particular mechanism of mutagenicity that may be an initiating event for cancer. However, such tests typically provide only supporting information about a pollutant's effects, as few tests have been developed that are specific to a particular effect or disease.

- **Structure-activity Relationships (SARs).** By comparing the molecular structure of a pollutant with that of others of known toxicity, toxic effects can sometimes be inferred, particularly if there is knowledge about the mechanism of action. This approach is often useful when examining the hazards associated with individual compounds within a class of related compounds (e.g., dioxins) or when identifying compounds for future study. Although structure-activity analyses are rarely a substitute for existing experimental or epidemiologic data, and represent a relatively uncertain basis for hazard identification, they are useful when experimental data are absent.

attendant dose/exposure levels) are described. While there may be no formal hierarchy, particular attention is given to effects that occur at relatively low doses or that may have particular relevance to human populations. The narrative description of the data base discusses factors such as the methodological strengths and weaknesses of individual studies (as well as the overall data base), the time period over which the studies were conducted (e.g., chronic vs. subchronic), routes of exposure, and possible biological mechanisms. In the course of this narrative, there is discussion of effects, which may range from severe frank effects that can cause

incapacitation or death to subtle effects that may occur at the cellular level but are early indicators of toxic effects. Not all effects observed in laboratory studies are subsequently judged to be adverse effects. The distinction between adverse and non-adverse effects is not always clear-cut, and considerable professional judgment is required in applying criteria to identify adverse effects. All of these observations are integrated into a presentation that gives a concise profile of the toxicological properties of the pollutant.

In addition to toxicity related to long-term exposures, many HAPs also can cause toxic effects after short-term exposures lasting from minutes to several hours. Indeed, for some pollutants acute exposures are of greater concern than chronic exposures. The hazard identification step for acute effects is comparable to that for chronic effects, with the primary difference being the duration of exposure. As with chronic exposures, the severity of effects from acute exposures may vary widely. The selection of a severity level for acute effects assessment may vary with the purpose of the assessment. While various EPA offices have addressed acute exposures across a variety of regulatory programs, Agency-wide guidance on how to assess toxic effects from short-term exposures is only recently being developed. This guidance for acute reference exposure (ARE) levels is intended to assist Agency acute risk assessment activities (EPA 1998g). Additionally, a discretionary federal advisory committee supported by EPA currently is assessing hazard and developing quantitative values (referred to as acute exposure guidance levels (AEGLs) for acute toxicity of specific chemicals (EPA 1997h), following guidance published by NRC (NRC 1993).

Cancer. The EPA's 1986 *Guidelines for Carcinogen Risk Assessment* (EPA 1986b) provide guidance on hazard identification for carcinogens. The approach recognizes three broad categories of data: (1) human data (primarily epidemiological); (2) results of long-term experimental animal bioassays; and (3) a variety of data on short-term tests for genotoxicity and other relevant properties, pharmacokinetic and metabolic studies, physio-chemical properties, and structure-activity relationships (SAR). In hazard identification of carcinogens under the 1986 guidelines, the human data, animal data, and "other" evidence are combined to characterize the weight of evidence regarding the agent's potential as a human carcinogen into one of several hierarchic categories.

- **Group A – Carcinogenic to Humans**: Applies when there are adequate human data to demonstrate the causal association of the agent with human cancer (typically epidemiologic data).

- **Group B – Probably Carcinogenic to Humans**: Agents with sufficient evidence (i.e., indicative of a causal relationship) from animal bioassay data, but either limited (i.e., indicative of a possible causal relationship, but not exclusive of alternative explanations) human evidence (Group B1), or with little or no human data (Group B2).

- **Group C – Possibly Carcinogenic to Humans**: Agents with limited animal evidence and little or no human data.

- **Group D – Not Classifiable as to Human Carcinogenicity:** Agents without adequate data either to suggest or refute the suggestion of the human carcinogenicity.

- **Group E – Evidence of Noncarcinogenicity for Humans**: Agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies (EPA 1986b).

In 1996, EPA proposed major revisions of the carcinogen hazard identification scheme. The proposed revision to the cancer risk assessment guidelines (EPA 1996b), which is expected to be finalized in 1999, focuses on narrative statements describing the main lines of evidence and their interpretation, in place of the current pre-defined hierarchical categories with alphabetic designations. Rather than the three-step process used under the 1986 guidelines of separately evaluating human evidence, evaluating animal evidence, and combining these judgments into an overall weight of evidence (while considering the short-term test data), the proposed guidelines suggest a single comprehensive evaluation process. This process stresses the explicit consideration of coherence of the various data elements into one scientific interpretation that evaluates, to the extent possible, how well the commonality of mode of carcinogenic action between human beings and the various test systems has been established. Emphasis is also placed on defining the qualitative conditions under which carcinogenic hazards might be expected. If warranted, limitations to the finding of carcinogenic hazard can be drawn based on route of exposure, necessity of some other factors for which tumorigenesis is necessary, and doses below which elevation of cancer risk is not expected. Key differences in the hazard identification step between the 1996 proposed revised cancer guidelines and the original 1986 guidelines are highlighted in **Exhibit 10**.

Dose-response Assessment

Dose-response assessment is the characterization of the relationship between the concentration, exposure, or dose of a pollutant and the resultant health or environmental effects. The nature of quantitative dose-response assessment varies among pollutants. Sufficient data often exist for criteria air pollutants, such as ozone or carbon monoxide, so that relatively complete dose-response relationships can be characterized. In such cases, there is no need for extrapolation to lower doses because adequate health effects data are available, often in humans, at environmental levels. Such is not the case for most air toxics. Most

DOSE-RESPONSE ASSESSMENT FOR MIXTURES

The EPA mixtures guidelines (EPA 1986c), which are currently in the process of being updated (EPA 1997d), indicate the following hierarchy for evaluating mixtures:

- Use toxicity data on the specific mixture of concern;
- If such data are not available, use toxicity information on a similar mixture; and
- If such data are not available, use toxicity information on the components of the mixture.

It is unlikely that mixtures of HAPs from sources under review for residual risk will have been studied as independent entities because of their variability. Thus, the default has been and will continue to be to evaluate data on the individual mixture components, in accordance with EPA's guidelines.

EXHIBIT 10
SUMMARY OF MAJOR DIFFERENCES IN THE HAZARD IDENTIFICATION STEP BETWEEN EPA'S 1986 GUIDELINES (EPA 1986b) AND 1996 PROPOSED GUIDELINES FOR CARCINOGEN RISK ASSESSMENT (EPA 1996b)

1986 Guidelines	1996 Proposed Guidelines
Weighing Evidence of Hazard	
▸ Decisions are based almost exclusively on tumor findings in animals and/or humans.	▸ Decisions take into account all available evidence (e.g., structure-activity relationships, mode of action).
▸ Human and animal evidence are evaluated separately and combined into the overall weight of evidence.	▸ All data are evaluated in a single comprehensive evaluation process.
Classification Descriptors	
▸ Substance is assigned a weight of evidence classification (A through E) regarding its potential to cause cancer in humans.	▸ A narrative statement with descriptors (e.g., "known/likely" to be carcinogenic) is developed for a substance, and includes information on the lines of evidence, exposure pathways, conclusions, and limitations.

epidemiologic and toxicologic data on HAPs typically result from exposure levels that are high relative to environmental levels.

In summary, dose-response assessment methods for HAPs generally consist of two parts. First is the evaluation of data in the observable range, and second is the extrapolation from the observable range to low doses/risks. Recent terminology refers to the result of analysis in the observable range as the "point of departure," from which extrapolation begins. The approaches used for evaluation in the observable range are similar for all types of effects, while the Agency's current extrapolation methods differ considerably for cancer and non-cancer effects.

Non-cancer Effects – Chronic. The inhalation RfC and oral RfD are the primary Agency consensus quantitative toxicity values for use in non-cancer risk assessment. The RfC or RfD is defined as an estimate, with uncertainty spanning perhaps an order of magnitude, of an inhalation exposure/oral dose to the human population (including sensitive subgroups) that is likely to be without appreciable risks of deleterious effects during a lifetime. The RfC or RfD is derived after a thorough review of the health effects data base for an individual chemical and identification of the most sensitive and relevant endpoint and the principal study(ies) demonstrating that endpoint. As discussed above under hazard identification, not all effects that can be observed in studies are determined to be adverse effects; a non-adverse effect would not be selected as the critical effect on which to base an RfC or RfD. Inhalation RfCs are derived according to the Agency's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA 1994e). The RfC or RfD should represent a synthesis

of the entire data array. The evaluation of and choice of data on which to base the RfC or RfD derivation are critical aspects of the assessment and require scientific judgment.

Derivation of the RfC or RfD begins with identification of the critical adverse effect from the available valid human and animal study data, followed by identification of a lowest-observed-adverse-effect level (LOAEL) or, preferably, a no-observed-adverse-effect level (NOAEL). The LOAELs or NOAELs from animal studies are converted to human equivalent concentrations (HECs) using dosimetric methods (described in EPA 1994e). The NOAEL[HEC] or LOAEL[HEC] from one or a few studies that is representative of the threshold region of observable effects is the key value gleaned from evaluation of the dose-response data. Recently, the benchmark dose (BMD) or benchmark concentration (BMC) approach (described below) has sometimes been used to effectively derive the LOAEL or NOAEL used as the "departure point" for extrapolation to the human exposure of interest. The RfC or RfD is then derived by consistent application of uncertainty factors (UFs) to account for recognized uncertainties in the extrapolation from the experimental data and exposure conditions to an estimate (the RfC or RfD) appropriate to the assumed human lifetime exposure scenario (EPA 1994e).

The standard UFs are applied as appropriate for the following extrapolations or areas of uncertainty:

- Laboratory animal data to humans;
- Average healthy humans to sensitive humans;
- Subchronic to chronic exposure duration;
- LOAEL to NOAEL; and
- Incomplete data base.

Other chemical-specific uncertainty factors (sometimes called modifying factors) may also be applied for individual HAPs depending on the existing health effects data set. The UFs that are generally applied range from a factor of three to an order of magnitude. The composite UF will depend on the number of extrapolations required. RfCs have been derived using composite UFs that range from 10 to 3,000, with most RfCs using factors of 100 to 1,000. The UF for animal to human extrapolation in RfC development often is less than an order of magnitude due to the dosimetric adjustments employed. It is also common that chemical-specific information is used to reduce the UF in other extrapolations. For example, the subchronic to chronic UF for acrylic acid was reduced because a comparison of two-week and 90-day studies showed minimal difference in the incidence or severity of effect, suggesting that there was little difference at various exposure durations. Likewise, the LOAEL to NOAEL extrapolation UF has been reduced for several RfC derivations because the effect at the LOAEL was very mild. In general, studies (e.g., Baird et al. 1996) have shown that the default UF of 10 may be conservative in many cases, and the UF is therefore a key parameter for examination in uncertainty analyses. When reductions in the UF are used, a factor of three is used as a convention because it is a half-order of magnitude on a logarithmic scale (i.e., $10^{1/2}$), rounded to one significant figure. It is also common to reduce the composite UF when four areas of

uncertainty are present, in recognition of the lack of independence of these areas. The result of this procedure, subject to peer review, is an RfD for oral (ingestion) exposure to an agent or an RfC for inhalation exposure. In addition to a numeric RfD or RfC, EPA also develops a degree of confidence statement (of either high, medium, or low).

The use of order-of-magnitude uncertainty factors for RfCs and RfDs and the definition of the RfC or RfD as having "uncertainty, spanning perhaps an order of magnitude" are indications of the general lack of precision in the estimates. The uncertainty resulting from any single area of extrapolation is not well understood or precisely defined. Current efforts to develop more rigorous statistical descriptions of the uncertainty in extrapolating from, for example, animals to humans or subchronic to chronic exposures may lead to a probabilistic method for assigning UFs. The current state-of-the-art, however, relies on point estimates of uncertainty and therefore results in point estimates of the RfC or RfD. The individual UFs are generally considered to be somewhat conservative, when they have not been reduced in conjunction with the availability of data relevant to the various extrapolations. It follows that the greater the overall magnitude of the UF (i.e., the more individual UFs that were combined to get the total UF), the more conservatism is included. The precision of "an order of magnitude" should be considered to apply on the average. Less precision would be implied in the case of an RfC with a greater UF (e.g., $\geq$1,000), and more precision would be suggested for RfCs with lower overall UFs (e.g., $\leq$100). The relative precision and the magnitude of the composite UFs will be important considerations in decisions involving comparisons of HQ for different chemicals and in assessing the hazard index (HI) for a mixture of chemicals.

Recently, the BMC/BMD approach has been used to supplement the approaches based on LOAELs and NOAELs. The BMD approach is an alternative to the NOAEL approach as a way to identify a dose associated with a given level of response, or a dose without appreciable effect based on experimental data. The BMD approach fits a dose-response curve to the data in the observed experimental range. A lower bound on the dose causing some specified level of risk above background (e.g., 10 percent) is calculated, and this dose value is used as a point of departure for the application of UFs in place of the experimental NOAEL or LOAEL. That is, it is taken as a standardized measure of a dose level near that at which an experimental response would no longer be expected to be evident using standard study designs. The BMD considers the entire data set, including the steepness of the dose-response relationship, accounts for the sample size, and does not depend on a single data point as does the NOAEL. A primary problem with a NOAEL is the wide range of risk that may be present at the NOAEL, depending on experimental design; the benchmark approach minimizes this problem. The benchmark approach has been used by EPA in several recent RfC and RfD assessments.

It should be noted that exposures above an RfD or RfC do not necessarily imply unacceptable risk or that adverse health effects are expected. Because of the inherent conservatism of the RfC/RfD methodology, the significance of exceedances must be evaluated on a case-by-case basis, considering such factors as the confidence level of the assessment, the

size of UFs used, the slope of the dose-response curve, the magnitude of the exceedance, and the number or types of people exposed at various levels above the RfD or RfC.

Non-cancer Effects – Acute. Methods for dose-response assessment of acute exposures are substantially similar to the approach for chronic exposure. Risk assessment for acute inhalation exposure is complicated by the steep concentration-response curves that are often observed, and because small differences in exposure duration (in some cases, a few minutes) need to be taken into account. Because increased exposure duration increases the incidence and severity of response, acute toxicity criteria or exposure guideline values are developed for a specified duration (e.g., one hour). An acute toxicity study providing well-characterized exposure and effects data for the exposure route of interest is used as the basis. Many acute toxicity studies only report on the incidence of death. It is preferred, however, to base the development of acute toxicity criteria on studies that evaluate additional endpoints, including clinical signs, clinical chemistry, and histopathology. For an inhalation criterion, the exposure duration of the study should ideally be the same as the one of interest (e.g., one hour). If significant interpolation across exposure durations is required, multiple studies are preferred to improve the quality of the interpolation. Such approaches based on applying uncertainty factors to acute toxicity data points (e.g., LOAEL, lower 95 percent confidence limit on effective concentration at 10 percent response (LEC_{10}), NOAEL) have been developed and used by various groups (see further discussion under following section, "Data Availability, Limitations, and Closing Data Gaps"). We are currently developing a new Agency method for acute dose-response assessment, the resultant value of which is termed an acute reference exposure (ARE) (EPA 1998g).

In developing the new Agency method, in addition to the use of either a LOAEL or NOAEL, or a BMC/BMD, an approach referred to as categorical regression is being evaluated. This approach allows the combination of data from different studies in order to evaluate the role of both exposure concentration *and* duration in producing the effect (EPA 1998g). Data are combined by expressing various effects on a common scale of severity and performing a regression analysis of severity versus concentration and duration. The results of a categorical regression analysis are used in the same way as a BMC/BMD or a NOAEL, i.e., as the departure point for extrapolation to the human exposure of interest. In the case of the NOAEL or the BMC/BMD, the departure point is a point estimate. In categorical regression, the departure point can be a line on a concentration versus time plot, with the result that any duration of acute exposure can be interpolated along that line. The line is actually a composite of likelihood estimates calculated from the regression results. For example, a concentration-time line indicating the 10 percent likelihood of observing a specific category of effect, termed an ECT_{10} line, could be generated that is analogous to a BMD_{10} or BMC_{10} as a point of departure. The appropriate approach for dose-response analysis will depend on the amount and quality of the available data. In general, the NOAEL, BMC/BMD, and categorical regression techniques have increasing data requirements, so the most appropriate approach will be dictated by the available data with the expectation that use of the data intensive categorical regression method may be

somewhat limited. After the best estimate of a point of departure is determined, the derivation of the ARE proceeds with the consistent application of UFs.

Cancer. The EPA's cancer risk assessment guidelines of 1986 adopted a default assumption that chemical carcinogens would exhibit risks at low doses (EPA 1986b). Extrapolation of cancer risk using the linearized multistage model, which results in a linear extrapolation of risk in the low dose region, was proposed as a reasonable upper-bound on risk, and this approach has been used for most chemicals with adequate data since then. However, as stressed in the *Proposed Guidelines for Carcinogen Risk Assessment* (EPA 1996b), when there are adequate mechanistic data to suggest that other models would be more appropriate to estimate low exposure risk, they may be used on a case-by-case basis. In the absence of such data, the assumption of response linearity is maintained although the modeling scheme has been simplified.

In cancer dose-response assessments relying on oral animal studies for which chemical-specific data are not available to guide the scaling of results to human equivalents, a default scaling factor based on the body mass raised to the 3/4 power of the test animals relative to humans is generally used to calculate a human equivalent dose.[9] For inhalation exposure studies, dosimetric methods such as those used in developing RfCs are generally used to calculate a HEC from animal data. Dose-response models such as the multistage model have historically been used to calculate upper-bound unit risk estimates (UREs). Typically, EPA has relied on the URE as a quantitative measure of potential cancer hazard. A URE represents an estimate of the increased cancer risk from a lifetime (assumed 70-year) exposure to a concentration of one unit of exposure. The URE for inhalation exposures is typically expressed as risk per $\mu g/m^3$ for air contaminants. The URE is a plausible upper-bound estimate of the risk (i.e., the risk is not likely to be higher but may be lower and may be zero).

Since the publication of the EPA's original cancer guidelines (EPA 1986b), considerable new knowledge has been developed regarding the processes of chemical carcinogenesis and the evaluation of human cancer risk. Currently, a revision of the cancer guidelines is in process (EPA 1996b) that represents a considerable departure from the original guidelines (see **Exhibit 11** for key differences in the dose-response assessment step between the two sets of guidelines). As mentioned above, a fundamental and important advance in the proposed revision is the distinction between linear and nonlinear modes of action. The cancer data in the observable range are analyzed using a dose-response model similar to the models used in the BMC approach for non-cancer effects. The LED_{10} (the 95 percent lower confidence limit on dose associated with the estimated 10 percent increase in tumor or tumor-related response) is proposed as a

[9] As specified in the July 5, 1992, *Federal Register* (EPA 1992d), "in the absence of adequate information on pharmacokinetic and sensitivity differences among species, doses of carcinogens should be expressed in terms of daily amount administered per unit of body mass raised to the 3/4 power. Equal doses in these units (i.e., in $mg/kg^{3/4}/day$), when experienced daily for a full lifetime, are presumed to produce equal lifetime cancer risks across mammalian species." This scaling method is assumed to be intermediate between scaling by body mass and scaling by body surface area.

EXHIBIT 11
SUMMARY OF MAJOR DIFFERENCES RELATED TO DOSE-RESPONSE ASSESSMENT BETWEEN EPA'S 1986 GUIDELINES (EPA 1986b) AND 1996 PROPOSED GUIDELINES FOR CARCINOGEN RISK ASSESSMENT (EPA 1996b)

1986 Guidelines	1996 Proposed Guidelines
▸ Default model used for linear dose-response relationships is the "linearized multistage" procedure.	▸ Biologically based dose-response models are used whenever data are sufficient. Recommended default approaches include the margin of exposure approach and linear extrapolation to zero dose, zero response.
▸ Dose-response evaluation is limited to carcinogenicity data.	▸ If appropriate, data on noncarcinogenic effects may be used to help characterize the carcinogenicity dose-response relationship.

possible point of departure for extrapolation, although other options are being considered. The method of extrapolation to lower doses from the point of departure differs depending on whether the assessment of the available data on the mode of action of the chemical indicates a linear or nonlinear mode of action. A linear extrapolation is generally appropriate when the evidence supports a mode of action of gene mutation due to direct DNA reactivity or another mode of action that is thought to be linear in the low dose region. For linear extrapolation, a straight line is drawn from the point of departure to the origin, and the risk at any concentration is determined by interpolation along that line. A linear mode of action also will serve as a default when available evidence is not sufficient to support a nonlinear extrapolation procedure, even if there is no evidence for DNA reactivity.

An assumption of nonlinearity is used when there is sufficient evidence to support a nonlinear mode of action. A nonlinear mode of action could involve a dose-response pattern in which the response falls much more quickly than linearly with dose, but still indicating risk at low doses. Alternatively, the mode of action may theoretically have a threshold if, for example, the cancer response is a secondary effect of toxicity or an induced physiological change which is a threshold phenomenon. In most cases, EPA will not try to distinguish between modes of action with a "true threshold" and those that are nonlinear through the origin, because data are rarely sufficient to make this determination. As a default science policy, nonlinear extrapolation to low doses will not be performed because there is no current basis to choose a model or determine the shape of the dose-response function. However, as more specific information on a HAP's mechanism of action becomes available and where the data are sufficient to support the use of alternative models, EPA will use them.

For carcinogens with nonlinear modes of action, the Agency has proposed a "margin-of-exposure" (MOE) approach to cancer risk assessment (EPA 1996b). The MOE approach has also be advocated as a method to harmonize cancer and non-cancer non-response assessment methodology (*Proposed Guidelines for Carcinogen Risk Assessment*, EPA 1996b; CRARM

report, CRARM 1997b). In the proposed MOE approach, the point of departure as described above is compared directly with the estimated exposure level (rather than having uncertainty factors applied), and the current understanding of the phenomena that may be occurring as exposure decreases below the observed data is considered. It is possible that the point of departure will be based on effects other than tumor data if, for example, the cancer response is determined to be secondary to a non-cancer effect.

In the proposal for this approach, the Agency recommends that additional dose-response information also be supplied to the risk manager. The information should include points such as the slope of the dose-response curve, the nature of the response, the human variability in sensitivity, persistence of the agent in the body, and relative sensitivity of humans and animals. The point of providing related information is to allow the risk manager to consider all aspects of the data to inform the decision about the appropriate MOE and the amount of reduction in risk associated with reduction in exposure below the point of departure. The endpoints relevant to the cancer assessment are determined based on a review of all relevant data.

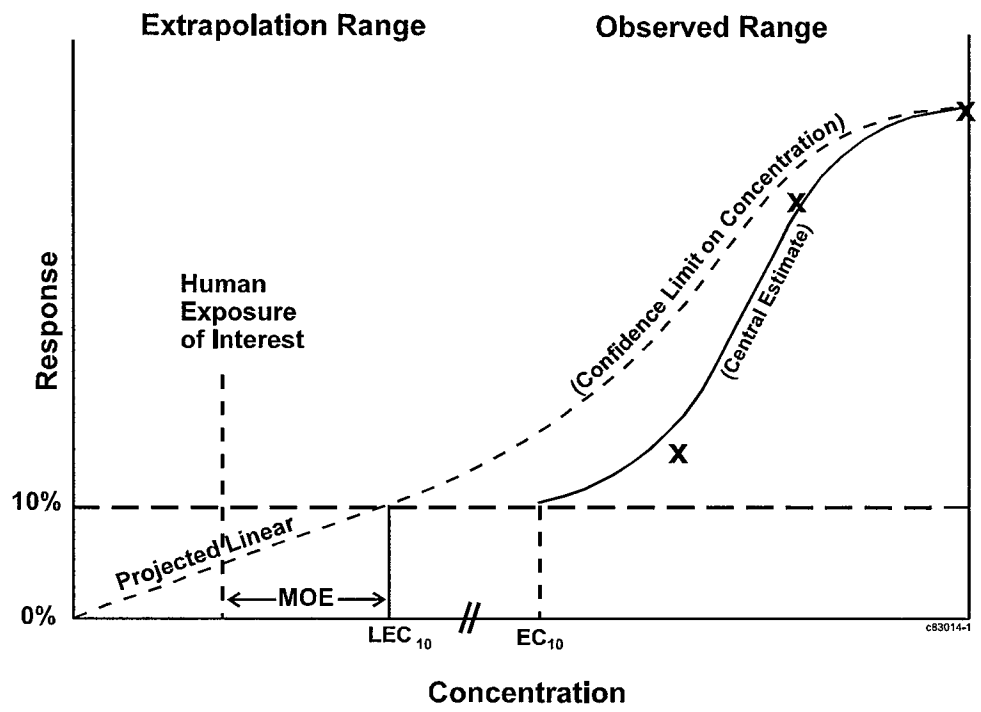
Linear Extrapolation. The dose-response approach for cancer-causing agents for which there is evidence of direct-acting genotoxicity is to model the data in the observable range to determine the point of departure (e.g., LEC_{10}). The only difference between the LEC_{10} approach and the BMC approach for non-cancer effects is that the cancer modeling may be done using a single default approach, rather than the evaluation of several models and statistical comparisons to determine the best-fitting model as currently proposed for non-cancer endpoints. Using the LEC_{10} as the point of departure, the low-concentration extrapolation is done by extending a straight line from the LEC_{10} to zero dose and zero risk (the origin). The risk at any exposure concentration is then determined using that line. **Exhibit 12** depicts the linear cancer dose-response curve being discussed. The linearity assumption implies, among other things, that some risk exists at low doses.

Nonlinear Extrapolation. The dose-response approach for nonlinear carcinogens is to model the data in the observable range in the same way as for linear carcinogens. Extrapolation from the point of departure (e.g., LEC_{10}) would involve an MOE analysis in which various other types of data would be considered to determine whether there is an adequate margin between the estimated exposures and the point of departure. This approach is qualitatively different than the linear extrapolation described above because the explicit consideration of exposure estimates moves it into the realm of risk characterization. Exhibit 12 also depicts the MOE approach being discussed.

Data Availability, Limitations, and Closing Data Gaps

Regardless of the endpoint of interest (acute, chronic non-cancer, or cancer effects), consensus toxicity criteria are preferred for conducting risk assessments. For chronic non-cancer and cancer criteria, the preferred source of data is EPA's IRIS. This data base provides toxicity criteria that have undergone internal peer review, and, for recent assessments, external peer

EXHIBIT 12
CANCER DOSE-RESPONSE CURVE



Source: Adapted from EPA 1996b

review, and have been approved Agency-wide. The toxicological basis for the criterion is provided, as well as other supporting data and information regarding the uncertainty in the assessment. Other chronic toxicity criteria that have undergone less rigorous internal Agency review are available in the Health Effects Assessment Summary Tables (HEAST), which may be consulted for residual risk assessments when data are unavailable in IRIS. For HAPs not having adequate toxicity information in IRIS, EPA will develop and follow a hierarchy of data sources, including various kinds of Agency health effects assessment documents, ATSDR toxicological profiles, and other sources. Consensus toxicity values for effects of acute exposures have been developed by several different organizations, and EPA is beginning to develop such values. The EPA also intends to develop and use a data source hierarchy for acute toxicity information. Consequently, we will not be relying exclusively on IRIS values, but will be considering all credible and readily available assessments. In more refined assessments, which may become the basis for a risk management regulatory decision, we will consider all credible and relevant toxicity information.

Significant progress is needed to improve the Agency's ability to comprehensively assess risks of the 188 HAPs. Assessments are currently available in IRIS for approximately two-thirds of the 188 HAPs, although these assessments may be incomplete. Inhalation assessment values (either cancer or non-cancer) are available for slightly less than half. Reliance on assessments from outside EPA, at least in initial screening-level assessments, provides inhalation assessment values (either cancer or non-cancer) for approximately 80 percent. The need to update assessments with newly available data as well as the need to round out the availability of assessments for all HAPs increases the importance of Agency activities to update IRIS (EPA 1998h). The Agency is in the final stages of a pilot program of improvements to IRIS, and is transitioning to full implementation of the improved system. Among the improvements, EPA has standardized the method for solicitation of scientific information from the public via a *Federal Register* notice and the use of rigorous external peer review procedures for both IRIS summaries and the new Toxicological Review documents. During fiscal year 1998, the Agency was able to update IRIS files for 10 substances and may increase that number during fiscal year 1999 and future years.

Chronic Non-cancer Effects Assessment. For chronic non-cancer risk assessment, the inhalation RfC and oral RfD are the primary quantitative consensus values used by EPA, the primary source for which is EPA's IRIS. The derivation of these values was discussed in detail in the dose-response section above. The RfC and RfD values in IRIS have undergone internal peer review, and, for recent assessments, external peer review, and have been approved Agency-wide. The toxicological basis for the values is provided, as well as other supporting data and information regarding the uncertainty in the assessment. As the IRIS assessments for some HAPs are less current than others, the Agency will evaluate the appropriateness of some assessments in light of more recent credible and relevant information.

To begin closing the gaps in human health effects toxicity data for HAPs, especially in IRIS, EPA has proposed a test rule for HAPs under section 4(a) of the Toxic Substances Control Act (TSCA) (EPA 1997i). Under the toxicity test rule, the Agency will require manufacturers and processors of certain HAPs to test these substances for specific health effects. The data collected under this test rule will be used in new or updated dose-response assessments for placement on IRIS. This regulatory mechanism will assist EPA in filling data gaps for other HAPs through future development of additional test rules. Improving the completeness of toxicity testing data sets used in HAP dose-response assessments assists in reducing the uncertainty in those assessments and any resultant risk assessments.

When chronic non-cancer toxicity criteria are not available from IRIS, several other sources may be consulted to obtain values for use in residual risk assessments. Some of these sources and criteria are summarized in **Exhibit 13**. These alternative sources use an approach similar to the approach used to derive RfC and RfD values for IRIS. If appropriate criteria are not available, the Agency may develop a provisional RfC or RfD using published EPA methodology.

EXHIBIT 13
EXAMPLES OF CHRONIC TOXICITY CRITERIA

Organization	Value	Definition and Basis
EPA/ORD	Integrated Risk Information System (IRIS) Reference Concentration (RfC)/Reference Dose (RfD) (EPA 1998i)	An RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime. Similarly, an RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime. The RfC/RfD values in IRIS have undergone rigorous review and received Agency-wide approval.
EPA/OSWER	Health Effects Assessment Summary Tables (HEAST) Reference Concentration (RfC)/Reference Dose (RfD) (EPA 1997j)	The RfC/RfD definitions are identical to those for the IRIS RfCs/RfDs. The HEAST is a comprehensive listing consisting almost entirely of provisional risk assessment information for oral and inhalation routes for chemicals of interest to Superfund, the Resource Conservation and Recovery Act (RCRA), and EPA in general. Although the values in HEAST have undergone review and have the concurrence of individual Agency program offices, they have not had enough review to be recognized as Agency-wide consensus information.
Agency for Toxic Substances and Disease Registry (ATSDR)	Chronic Minimal Risk Level (MRL) (ATSDR 1998)	An MRL is an estimate of the daily human exposure (inhalation or oral) to a hazardous substance that is likely to be without appreciable risk of non-cancer health effects over a specified duration of exposure. The intermediate exposure duration is 15-364 days, and the chronic exposure duration is 365 days and longer. MRLs are derived similarly to RfDs and RfCs; however, the ATSDR protocol uses different endpoints than EPA. MRLs are developed by ATSDR as substance-specific health guidance (i.e., screening) levels to identify contaminants of concern at hazardous waste sites. The data undergo a rigorous review process, including internal ATSDR reviews, peer reviews, and public comment periods.

NOTE: Criteria are available from other sources, including State agencies such as the California Environmental Protection Agency, and may be considered as needed.

Acute Non-cancer Effects Assessment. EPA efforts are underway to develop acute toxicity criteria with a consistent and sound scientific basis, including the AREs being developed by EPA's ORD (EPA 1998g). The methodology was reviewed by EPA's SAB in June 1998 and is being revised to address comments received. When they become available, AREs will be the preferred values to be used for residual risk assessments. AEGLs are being developed by the National Advisory Committee for AEGLs for Hazardous Substances (NAC/AEGL Committee), a discretionary federal advisory committee. The NAC/AEGL committee follows procedures consistent with NRC guidelines (NRC 1993). Proposed AEGL values for the first 12 chemicals have been published for public comment (EPA 1997h). Acute toxicity criteria known as emergency response planning guidelines (ERPGs) have been developed by the American Industrial Hygiene Association (AIHA) for various severities of effects (AIHA 1998). In the late

1980s, EPA developed LOCs (levels of concern) for extremely hazardous substances (EHSs) regulated under section 302 of the Emergency Planning and Community Right-to-Know Act (EPA et al. 1987). These and selected other acute toxicity criteria are summarized in **Exhibit 14**.

EXHIBIT 14
EXAMPLES OF ACUTE TOXICITY CRITERIA

Organization	Value	Definition and Basis
EPA/ORD	Acute Reference Exposure (ARE) (EPA 1998g)	Exposure (concentration and duration of 1-24 hours) that is not likely to cause adverse effects in the general population. Based on NOAEL/LOAEL or surrogate and UFs. Exposure levels at which increased mild (adverse effects level [AEL]-1), moderate/severe (AEL-2), or frank (FEL) effects occur also considered. Method under development.
Federal Interagency Group (includes EPA)	Acute Exposure Guidance Level (AEGL) (NRC 1993, EPA 1997h)	Under development by Federal Advisory Committee Act (FACA) committee. First 12 proposed AEGLs recently published (EPA 1997h). Concentrations for 1-8 hour exposure of the general population. Levels that are expected to protect from discomfort (AEGL-1), disability (AEGL-2), or life-threatening effects or death (AEGL-3). Based on NOAEL/LOAEL or surrogate and uncertainty factors (UFs).
American Industrial Hygiene Association (AIHA)	Emergency Response Protective Guideline (ERPG) (AIHA 1998)	Concentrations for exposure of the general population for durations up to 1 hour. Levels expected to protect individuals from other than mild, transient (ERPG-1), irreversible or serious (ERPG-2), or life-threatening (ERPG-3) effects. Based on weight of evidence and professional judgment.
Agency for Toxic Substances and Disease Registry (ATSDR)	Minimal Risk Level (MRL) (ATSDR 19xx)	For inhalation or oral exposure of the general population for up to 14 days, value at which adverse health effects not expected. Derived using NOAEL/LOAEL and UFs, similar to RfCs/RfDs.
National Research Council (NRC)	Short-term Public Emergency Guidance Level (SPEGL) (NRC 1986)	Ceiling concentration for an unpredicted single exposure (1-24 hours) designed to protect the general population. Based on professional judgment.
EPA/OPPT	Level of Concern (LOC) (EPA et al. 1987)	Concentration that may result in serious irreversible health effects or death in the general population after exposure for a relatively short (1-hour) period. Based on 0.1 x the IDLH (immediately dangerous to life and health) level or surrogates. (Note: The LOC is no longer preferred for emergency planning (EPA 1996e); AEGLs or ERPGs should be used if available.)

NOTE: Criteria are available from other sources, including State agencies such as the California Environmental Protection Agency, and may be considered as needed.

As for the chronic criteria, consensus values are preferred when available. If a suitable consensus value is not available, the Agency may derive a provisional value from acute toxicity data.

Cancer Assessment. As in the case of chronic non-cancer assessments, IRIS is the primary source of Agency consensus criteria. The derivation of these values was discussed in detail in the dose-response section above. The values in IRIS have undergone internal peer review, and, for recent assessments, external peer review, and have been approved Agency-wide. The toxicological basis for the values is provided, as well as other supporting data and information regarding the uncertainty in the assessment. As the IRIS assessments for some HAPs are less current than others, the Agency will evaluate the appropriateness of some assessments in light of more recent credible and relevant information. The EPA HEAST (described in Exhibit 13), as well as outside sources including State agencies, will also be consulted as needed.

The cancer criterion may be qualitative, in the form of a classification regarding the strength of the evidence concerning a chemical's carcinogenicity. Under the 1986 cancer guidelines, this classification might be "B2, probable human carcinogen based on sufficient evidence from animal studies." Under the proposed 1996 cancer guidelines, a chemical might be classified as "likely to be a human carcinogen by any route of exposure." These classifications represent the hazard identification phase. A dose-response assessment is also needed for any quantitative risk assessment. For cancer, this is typically expressed as the cancer risk per unit dose, or slope factor. If a consensus cancer criterion is not available from the hierarchy of sources, a provisional value may be derived. In order to derive a cancer slope factor, data are needed from a well-conducted lifetime carcinogenicity study, in which an adequate number of tissues were evaluated histopathologically, and treatment-related cancer was observed. A sufficient number of animals should have been used (generally 50/sex/dose), and the incidence and type of tumor and other histopathologic lesions should have been reported. Using the cancer incidence data, a linear extrapolation to zero from a point of departure is then used to calculate the cancer risk per unit dose. Data on a chemical's pharmacokinetics, its genotoxicity, and other information on its possible mode of action can be used to refine the assessment.

As is described previously, cancer dose-response assessments are not currently available (within or outside EPA) for all HAPs. We have activities underway to increase the HAP coverage in IRIS and to collect the toxicity data for these assessments.

3.4.2 Ecological Effects

In ecological effects characterization, risk assessors evaluate the relationship between HAP exposure and adverse effects on the ecological assessment endpoints which might have been identified at the population, community, or ecosystem level. A variety of sources of ecological effects data can be used, such as field studies, laboratory studies, and SARs (see **Exhibit 15**). The ecological effects characterization identifies causal information linking exposure to the HAP with relevant observed ecological effects and determines the nature and intensity of the effects and, if appropriate, the time scale for recovery after exposure ceases. The effects estimates can be either point estimates of a specified effect level (e.g., a 20 percent response level) or probabilistic estimates describing the entire stressor-response curve.

EXHIBIT 15
SOURCES OF INFORMATION FOR ECOLOGICAL EFFECTS

Various types of original data are used for ecological effects characterization, some of which are common to the human health effects data base.

- **Human Health Data Base.** With the exception of epidemiological data and controlled human exposures, the toxicological data which are used in the hazard identification and dose-response steps of human health assessment are also relevant to ecological effects, specifically for mammalian wildlife (see Exhibit 9).
- **Laboratory Studies.** Due to the limitations and expense of field studies and microcosm studies, most risk assessors rely on laboratory ecotoxicology studies. These studies are typically easier to conduct, and effects can be directly linked to exposure to a single HAP. There is uncertainty, however, in extrapolating the results from standard laboratory species to the wide array of species in the environment. Additionally, in most cases, laboratory studies are not designed to assess effects on populations, communities, and ecosystems.
- **Field Studies.** Studies of wildlife, populations, communities, and ecosystems exposed to HAPs in natural settings can provide valuable information on the effects of HAPs. Field data can be valuable in demonstrating the presence or absence of a cause-effect relationship that can provide a basis for prioritization or for recognizing the efficacy of a risk reduction action. In many cases, however, wildlife are exposed to numerous types of stressors (chemical and non-chemical), and the effects of individual HAPs can be difficult to isolate. In addition, field studies are conducted infrequently due to the significant time and resources required.
- **Microcosm Studies.** Studies on the exposure of multi-species and multi-media enclosed experimental systems to HAPs can control some of the uncertainty associated with multiple stressor exposure in field studies. These studies can provide information about food web dynamics and the interactions of populations of organisms. As with field studies, microcosm studies are time and resource intensive and, therefore, are relatively uncommon.
- **SARs.** In the absence of adequate ecotoxicology studies, scientists may rely on SARs. By using SARs, the toxic effects of a HAP can be inferred based on the similarity of its chemical structure to a chemical whose ecotoxicity is better understood. Types of SARs include: quantitative SARs (QSARs), qualitative SARs, and best analog SARs.

In the case of air toxics, ecological impacts can result from exposure to airborne HAPs (e.g., via inhalation) or exposure to HAPs deposited or transferred to other environmental media (e.g., water, soils). The HAP emissions can be assessed for both primary and secondary effects. Primary effects (e.g., lethality, reduced growth, neurological/behavioral and impaired reproduction) result from exposure of aquatic and terrestrial organisms to HAPs. An extreme example of a primary effect might be deaths of waterfowl caused by an accidental release of an extremely toxic chemical. HAPs which accumulate in plant and animal tissue provide a well known example of a direct harmful effect on wildlife. During the 1950s and 1960s, DDT built up in the wild food chain such that it caused thinning of eggshells of top predators such as bald eagles and brown pelicans, which dramatically reduced the birds' hatching success. The populations of these birds plummeted, driving them to the brink of extinction.

Secondary effects are the result of HAP action on supporting components of the ecosystem (e.g., habitat destruction, loss of prey, and nutrient imbalances). These secondary effects occur through biological interaction of one or more species' populations with individuals or populations which have been primarily affected. For example, exposure to a toxic air

pollutant may adversely effect one or more species of microscopic algae, bacteria, or fungus, which can adversely affect an ecosystem's nutrient cycling and primary production. This can lead to an alteration in the abundance, distribution, and age structure of a species or population dependent on these microscopic organisms which can then lead to changes in competition and food web interactions in other species. These ecosystem effects can be propagated to still other populations, affecting their presence or representation within the ecosystem. A relatively simple example of secondary effects involves the aerial application of pesticides in Canada which dramatically reduced the population of an aquatic insect. This impact to the insect population indirectly affected wild ducklings in the ecosystem which depend on the insects as a food supply (Sheehan et al. 1987).

Both primary and secondary effects may occur within the same time frame of exposure, but secondary effects tend to be long lasting and can persist well after the direct effects have been eliminated because of the interrelationships among species in an ecosystem.

The HAP emissions also can be assessed for both local and regional impacts. Local impacts, which apply to most HAPs, may be short-term or long-term and affect receptors near the source. Regional impacts, which apply primarily to persistent and bioaccumulative HAPs, are most often long-term and generally affect organisms both near to and distant from the source.

In assessing the potential for estimated exposures to pose environmental risks, the available data relevant to the chosen assessment endpoints are reviewed and a measure of effect is determined. Criteria (e.g., point estimates of thresholds for ecological effects) may be calculated for site-specific ecological receptors depending on the importance of those receptors to the local ecosystem, or for an endpoint not previously evaluated. For example, while some criteria may be based on survival, growth, and reproductive success of a population, criteria protective of a threatened or endangered species, a valuable game species (e.g., trout), or an ecologically key species (e.g., wolf) might be based on an endpoint that is relevant to individual organism health (e.g., a neurological deficit) rather than to population maintenance. On the other hand, criteria based on higher effect levels (e.g., 20 to 50 percent or higher of the population is affected) might be appropriate for species for which great functional redundancy exists in the ecosystem (e.g., different herbaceous plants; see Lawton and Brown 1994). The "scaling up" approach to analysis, inherently assumes that data evaluated at the individual or population level are applicable to higher scales (e.g., community, ecosystem) or broader scales (e.g., landscape, watershed, or ecosystem). As we develop more fully our methods for ecological risk assessment, we will be carefully considering this issue.

Criteria may be developed for each combination of environmental medium and ecological community described by the generic assessment endpoints in the conceptual model. For a persistent HAP that might partition into all environmental media, criteria may be needed for all of the following media/receptor combinations:

- Air/terrestrial animals exposed via inhalation;
- Air/plants with their foliage exposed to the air;
- Water/aquatic biota exposed via direct contact with water;
- Sediments/benthic aquatic biota exposed via direct contact with sediments;
- Soil/soil macro- and micro-invertebrates; and
- Soil/plants.

For each medium/receptor combination identified above, the criteria are usually expressed as a concentration of the HAP in the environmental medium. EPA ambient water quality criteria (AWQC) for the protection of aquatic life are an example used by the Agency's Office of Water in implementing the water quality protection sections of the CWA.

For a persistent HAP that might also bioaccumulate in plants or animals, a RfD considered protective of wildlife that feed on those plants or animals would be needed along with information on food ingestion rates for sensitive and most exposed animal species and information on the degree of bioaccumulation in appropriate trophic components. Examples of that approach for aquatic systems can be found in the Great Lakes Water Quality Initiative (GLWQI) for mercury, DDT, PCBs, and 2,3,7,8-TCDD (EPA 1995d,e) and for terrestrial systems in the EPA methods of assessing exposures to combustor emissions (EPA 1993b).

Development of stressor-response curves, instead of point estimates of effect, can provide more information for and flexibility in evaluating risks. For example, stressor-response curves can allow a description of the areal extent of a community that might be affected to differing degrees (e.g., 40 percent mortality of soil invertebrates over 10 acres, 20 percent mortality over the surrounding 100 acres, and less than 10 percent mortality of soil invertebrates in areas beyond those 110 acres).

Data Availability, Limitations, and Closing Data Gaps

EPA's identification of appropriate criteria for use in the air toxics program and specifically in residual risk analyses is an ongoing effort. Currently available criteria are being evaluated to determine their applicability in residual risk analysis. The screening level of analysis may use conservative criteria derived from no-observed-adverse-effect levels (NOAELs) for a most sensitive species for the community in question. This reliance on a 'bottom up' approach, which is similar to that relied upon in derivation of EPA water quality criteria for the protection of aquatic life, is assumed to be more likely to overestimate rather than underestimate risk. Other options are available for more refined analyses. And analyses for risk management/risk reductions under residual risk would also take into account costs, safety, energy, and other relevant factors, as specified under the CAA.

If appropriate ecotoxicity criteria are not available for a specific HAP, criteria may be developed, if adequate toxicity data are available (types of data are described in Exhibit 15). The

most appropriate laboratory tests are those that measure effects on survival, growth, and reproduction.

Although some of the animal toxicity data used for human health assessment provide data for mammalian effects assessment, it should be stated that data are lacking for effects endpoints, especially for plants, birds, and wildlife. Data from field studies are also not widely available. Additionally, there is a paucity of established criteria for environmental effects. There are no data sets comparable to the IRIS or HEAST data bases for human health values. As part of our tool and methodology development, we intend to identify an appropriate methodology for development of ecological criteria. An example of ecological criteria the Agency has developed are the ambient water quality criteria for the protection of aquatic life derived under the Clean Water Act. Until we identify the appropriate criteria or criteria methodology for air toxics assessments, the available effects data (e.g., EPA's AQUIRE, TERRETOX, and PHYTOTOX data bases (EPA 1998j)) are considered appropriate for use in screening-level assessments, while more refined assessments may require completion of more refined tools and the collection or compilation of additional data.

3.5 Risk Characterization

The final step in the risk assessment process is the risk characterization, in which the information from the previous steps is integrated and an overall conclusion about risk is synthesized that is complete, informative, and useful for decision-makers. The nature of the risk characterization will depend on the information available, the regulatory application of the risk information, and the resources (including time) available. In all cases, however, major issues associated with determining the nature and extent of the risk should be identified and discussed. Further, EPA's March 1995 *Policy for Risk Characterization* (EPA 1995f) specifies that a risk characterization "be prepared in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope prepared across programs in the Agency." EPA's 1995 *Guidance for Risk Characterization* (EPA 1995a) lists several guiding principles for defining risk characterization in the context of risk assessment. The three principles with respect to the information content and uncertainty aspects of risk characterization are as follows (EPA 1995a).

(1) **The risk characterization integrates the information from the hazard identification, dose-response, and exposure assessments, using a combination of qualitative information, quantitative information, and information regarding uncertainties.** A good characterization should include different kinds of information from all portions of the foregoing assessment, carefully selected for reliability and relevance.

(2) **The risk characterization includes a discussion of uncertainty and variability.** The risk assessor must distinguish between variability (arising from true heterogeneity) and uncertainty (resulting from a lack of knowledge).

(3) **Well-balanced risk characterizations present risk conclusions and information regarding the strengths and limitations of the assessment for other risk assessors, EPA decision-makers, and the public.** "Truth in advertising" is an integral part of the characterization, discussing all noteworthy limitations while taking care not to become mired in analyzing factors that are not significant.

3.5.1 Human Health Effects

The 1995 *Guidance for Risk Characterization* (EPA 1995a) identifies several guiding principles, shown in **Exhibit 16**, with respect to descriptions of risk.

EXHIBIT 16
GUIDING PRINCIPLES WITH RESPECT TO RISK DESCRIPTORS

- **Information about the distribution of individual exposures is important to communicating the results of a risk assessment.** Both high-end and central tendency descriptors are used to convey the variability in risk levels experienced throughout the population.
- **Information about population exposure leads to another important way to describe risk.** Both a probabilistic number of cases (or environmental impacts) and an expected percentage of the exposed population (or ecological resource) with risk greater than a certain level are valuable ways to present information.
- **Information about the distribution of exposure and risk for different subgroups of the population are important components of a risk assessment.** Highly susceptible individuals or areas should be identified as well as those highly exposed, when possible.
- **Situation-specific information adds perspective on possible future events or regulatory options.** Consideration of alternative scenarios when conducting risk assessment can aid in risk management decisions.
- **An evaluation of the uncertainty in the risk descriptors is an important component of the uncertainty discussion in the assessment.** Both quantitative and qualitative evaluations of uncertainty can be useful to users of the assessment.

Integration of Exposure and Effects Analyses

Risk assessments are intended to address or provide descriptions of risk to: (1) individuals exposed at average levels and those in the high-end portions of the risk distribution; (2) the exposed population as a whole; and (3) important subgroups of the population such as highly susceptible groups or individuals (e.g., children), if known.

Individual Risk. Individual risk predictions are intended to estimate the risk borne by individuals within a specified population or subpopulation. These predictions are used to answer questions concerning the affected population, the risk levels of various groups within the population, and the average or maximum risk for individuals within the populations of interest.

- *Central Tendency Estimates of Risk* are intended to give a characterization of risk for the typical situation in which an individual is likely to be exposed. This may be either the arithmetic mean risk (average estimate) or the median risk (median estimate), either of which should be clearly labeled (EPA 1992a).

- *High-end Estimates of Risk* are intended to estimate the risk that is expected to occur in a small but definable segment of the population. The intent is to "convey an estimate of risk in the upper range of the distribution, but to avoid estimates which are beyond the true distribution. Conceptually, high-end risk means risk above about the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest risk" (EPA 1992a).

Population Risk. Population risk predictions are intended to estimate the extent of risk for the population as a whole. This typically represents the sum total of individual risks within the exposed population.

Sensitive or Susceptible Subpopulations. Risk predictions for sensitive subpopulations are a subset of population risks. Sensitive subpopulations consist of a specific set of individuals who are particularly susceptible to adverse health effects because of physiological (e.g., age, gender, pre-existing conditions), socioeconomic (e.g., nutrition), or demographic variables, or significantly greater levels of exposure (EPA 1992a). Subpopulations can be defined using age, race, gender, and other factors. If enough information is available, a quantitative risk estimate for a subpopulation can be developed. If not, then any qualitative information about subpopulations gathered during hazard identification should be summarized as part of the risk characterization.

Because cancer and non-cancer dose-response assessment methods are currently quite different, risk characterizations also differ and are discussed separately.

Non-cancer Effects. Unlike cancer risk characterization, non-cancer risks typically are not expressed as a probability of an individual suffering an adverse effect. Instead, the potential for non-cancer effects is evaluated by comparing an estimated exposure level over a specified period of time (e.g., lifetime) with a reference level such as an RfC (described in Section 3.4.1).

"Risk" for non-cancer effects typically is quantified by comparing the exposure to the reference level as a ratio. The resultant HQ can be expressed as an equation, where HQ = exposure/reference level. Exposures or doses below the reference level (HQ<1) are not likely to be

HAZARD QUOTIENTS AND HAZARD INDICES

The hazard quotient (HQ) is the ratio of the estimated exposure to the health criterion level for a given chemical. For example, for chronic inhalation exposure, the health criterion could be the RfC. If the HQ is less than 1, the RfC is not exceeded and health effects are unlikely. The hazard index (HI) is the sum of the HQs for each chemical considered to have a similar mechanism of action in a mixture. The HI (for a mixture of i compounds) may be calculated as: $HI = HQ_1 + HQ_2 + ...+ HQ_i$. If the HI is <1, health effects are unlikely.

associated with adverse health effects. With exposures increasingly greater than the reference level (i.e., HQs increasingly greater than 1), the potential for adverse effects increases. The HQ, however, should not be interpreted as a probability. Comparisons of HQs across substances may not be valid, and the level of concern (LOC) does not increase linearly as exposures approach or cross the reference level. This is because of the differences among reference levels in their derivation and the fact that the slope of the dose-response curve above the benchmark can vary widely depending on the substance and type of effect.

While some potential environmental hazards may involve significant exposure to only a single compound, exposure to a mixture of compounds that may produce similar or dissimilar non-cancer health effects is more common. In a few cases, reference levels may be available for a chemical mixture of concern or for a similar mixture. In such cases, risk characterization can be conducted on the mixture using the same procedures used for a single compound. However, non-cancer health effects data are usually available only for individual compounds within a mixture. In screening-level assessments for such cases, a conservative HI approach is sometimes used (see text box above). This approach is based on the assumption that even when individual pollutant levels are lower than the corresponding reference levels, some pollutants may work together such that their potential for harm is additive and the combined exposure to the group of chemicals poses greater likelihood of harm. Some groups of chemicals can also behave antagonistically, such that combined exposure poses less likelihood of harm, or synergistically, such that combined exposure poses harm in greater than additive manner. The assumption of dose additivity is most appropriate to compounds that induce the same effect by similar modes of action (EPA 1986c). As with the HQ, the HI should not be interpreted as a probability of risk, nor as strict delineation of "safe" and "unsafe" levels (EPA 1986c; EPA 1989c). Rather the HI is a rough measure of potential for risk and needs to be interpreted carefully. Although the HI approach encompassing all chemicals in a mixture may be appropriate for a screening-level study (EPA 1989c), it is important to note that application of the HI equation to compounds that may produce different effects, or that act by different mechanisms, could overestimate the potential for effects. Consequently, in a refined assessment, it is more appropriate to calculate a separate HI for each non-cancer endpoint of concern when mechanisms of action are known to be similar (EPA 1986c).

Cancer. Risks for cancer are generally expressed as either individual risks or population risks. The distribution of exposures and individual risks within a given population can also be presented, providing an estimate of the number of people exposed to various predicted levels of risk. The Agency's risk characterization guidelines recommend that risk assessments describe individual risk, population risk, and risk to important subgroups of the population such as highly exposed or highly susceptible groups (EPA 1995a). For air toxics emissions, individual or population cancer risks can be calculated by multiplying the corresponding exposure estimate by the unit risk estimate (URE). Cancer risk is defined as the upper-bound probability of contracting cancer following exposure to a pollutant at the estimated concentration over a 70-year period (assumed human lifespan). This predicted risk focuses on the additional risk of cancer predicted from the exposure being analyzed, beyond that due to any other factors.

Estimates of risk are usually expressed as a probability represented in scientific notation as a negative exponent of 10. For example, an additional risk of contracting cancer of 1 chance in 10,000 (or one additional person in 10,000) is written as $1x10^{-4}$. Because UREs are typically upper-bound estimates, actual risks may be lower than predicted.

Population risk is an estimate that applies to the entire population within the given area of analysis. Each estimated exposure level is multiplied by the number of people exposed to that level and by the URE. For the great majority of HAPs for which the unit risk estimate is an "upper confidence level" value, this provides an upper-bound prediction of cancer risk for that group after a 70-year exposure to that level. The risks for each exposure group are summed to provide the excess cancer cases predicted in the entire exposed population. This 70-year population risk estimate is sometimes divided by 70 to obtain an upper-bound prediction of the number of cancer cases per year.

When calculating individual or population risk, it is important to check the consistency and validity of key assumptions, such as the averaging period for exposure, the exposure route, absorption adjustments, and spatial consistency.

People are often exposed to multiple chemicals rather than a single chemicals. In those few cases where cancer potency values and UREs are available for the chemical mixture of concern or for a similar mixture, risk characterization can be conducted on the mixture using the same procedures used for a single compound. However, cancer dose-response assessments and UREs are usually available only for individual compounds within a mixture. Consequently, in screening-level assessments of carcinogens for which there is an assumption of a linear dose-response, the cancer risks predicted for individual chemicals may be added to estimate total risk. This approach is based on an assumption that the risks associated with individual chemicals in the mixture are additive. The assumption of additivity is generally considered conservative. In more refined assessments, the chemicals being assessed need to be evaluated for this concern. The following equation estimates the predicted incremental individual cancer risk, assuming additivity, for simultaneous exposures to several carcinogens:

$$Risk_T = Risk_1 + Risk_2 + ... + Risk_i$$

where:

R_T = the total cancer risk (expressed as an upper-bound risk of contracting cancer over a lifetime)

R_i = the risk estimate for the i^{th} substance.

A variation of the additivity approach is used for some mixtures of structurally similar carcinogens for which cancer slope factors (i.e., measures of potency) are not available for all mixture components. For carcinogenic dioxins and furans, for example, a toxic equivalency factor (TEF) approach is used as described in EPA's dioxin reassessment document (EPA

1994f). In this approach, which has an underlying assumption of additivity across mixture components, the cancer potency of certain dioxin and furan congeners is estimated relative to 2,3,7,8-TCDD based on other toxicity information that is available for all the congeners (e.g., LD_{50}). Then, TEFs based on these relative cancer potencies are used to adjust the exposure concentrations of mixture components, which are subsequently summed into a single exposure concentration for the mixture. That exposure concentration based on TEFs is then used, along with the 2,3,7,8-TCDD slope factor, to estimate cancer risks for the mixture.

For carcinogens being assessed based on the assumption of nonlinear dose-response, the MOE approach may be considered, consistent with the proposed revision of EPA's cancer guidelines (EPA 1996b). As described in Section 3.4.1, the MOE approach leaves the decision about the appropriate reduction in exposure compared to the point of departure (i.e., the observable toxicity data) up to the risk manager. An in-depth MOE analysis would be made in consideration of factors that could include the steepness of the dose-response curve, persistence of the compound in the body, known human variability in response, or demonstrated human sensitivity as compared with experimental animals. In a typical case, the point of departure derived from modeling the observable data would be a tumor incidence of 10 percent (e.g., risk of 1 in 10). If the chemical fits a linear mode of action, a reduction in the dose of 1,000 would result in an estimated risk of 1 in 10,000. For a nonlinear mode of action, a reduction of the same magnitude would lead to a much lower risk because of the nonlinearity in the dose-response slope. If the mode of action includes a threshold below which there is no risk of cancer, such a reduction could lead to a zero cancer risk.

Since neither thresholds nor risk are explicitly estimated, there is no analogous form of the simple dose addition approach that is amenable to assessment of mixtures of nonlinear carcinogens. Since the MOE analysis is done on a case-by-case basis, the determination of the appropriate "acceptable" MOE for each component would be required before a mixtures assessment could be performed. It is also not clear how the MOE approach should handle effects in different target organs or with different modes of action. A consideration of the mode of action that leads to the conclusion that the nonlinear dose-response evaluation is appropriate can also provide information relevant to whether nonlinear carcinogens should be considered additive. While the Agency's current mixtures guidelines (EPA 1986c) do not address nonlinear carcinogens, they generally recommend the assumption of additivity for carcinogens unless contrary information is available. Carcinogenic substances showing nonlinear modes of action through unrelated mechanisms or in different tissues would not generally be combined.

Interpretation and Presentation of Risks

In the risk characterization step of final assessments under residual risk, the estimates of health risk will be presented in the context of uncertainties and limitations in the data and methodology. Additionally, information relevant to public health context of the residual risk will be presented. This may include, as available, information on relevant health effects occurring in the study population. Available epidemiological studies or other human health data will be

discussed and presented along with a summary of the hazard identification and dose-response information for the HAPs being assessed. Uncertainties and limitations related to the hazard identification and dose-response assessment may also be discussed. Uncertainty analyses and the presentation of uncertainties is discussed in more detail in Section 4.2.3.

The degree to which all types of uncertainty need to be quantified and the amount of uncertainty that is acceptable varies. For a screening-level analysis, a high degree of uncertainty is often acceptable, provided that conservative assumptions are used to bias potential error toward protecting human health. Similarly, a region-wide or nationwide study will be more uncertain than a site-specific one. In general, the more detailed or accurate the risk characterization, the more carefully uncertainty needs to be considered.

On May 15, 1997, EPA issued a document entitled *Policy for Use of Probabilistic Analysis in Risk Assessment* (EPA 1997k). It also issued an accompanying document entitled *Guiding Principles for Monte Carlo Analysis* (EPA 1997c). The policy and guiding principles are designed to support the use of various quantitative techniques for characterizing variability and uncertainty, a critical part of a complete risk characterization. The policy establishes conditions that are to be satisfied by risk assessments that use probabilistic techniques. These conditions relate to the good scientific practices of clarity, consistency, transparency, reproducibility, and the use of sound methods. **Exhibit 17** provides the conditions for an acceptable risk assessment that uses probabilistic analyses techniques. EPA's position, as stated in these documents, is "that such probabilistic analysis techniques as Monte Carlo analysis, given adequate supporting data and credible assumptions, can be viable statistical tools for analyzing variability and uncertainty in risk assessments."

Data Availability, Limitations, and Closing Data Gaps

The NRC, in its recent review of EPA's risk assessment methodology for HAPs (NRC 1994), recommended that uncertainty and variability should be quantified and the distinction between uncertainty and variability maintained throughout the assessment. A model under development by EPA for air toxics risk assessments, TRIM, will do this explicitly. In the interim, a Monte Carlo assessment is sometimes conducted on the risk estimates produced by HEM or other methods. At present, such assessments primarily address variability, while uncertainty is largely described qualitatively. The variability assessment considers variation in such factors as the number of years residents occupy their primary residences, number of hours per day people are at home, breathing rates across the exposed population, the amount of ambient pollution that infiltrates to the indoor microenvironment, and certain meteorological variables. Thus, the results of the assessment may be expressed in probabilistic terms, potentially providing the risk manager and the affected public with more information than was previously provided. However, care must be taken in the interpretation of such analyses, as they are only as reliable as the underlying data and assumptions. Uncertainty in risk assessment is discussed further in Section 4.2.3.

EXHIBIT 17
CONDITIONS FOR AN ACCEPTABLE RISK ASSESSMENT THAT USES PROBABILISTIC ANALYSIS TECHNIQUES

- The purpose and scope of the assessment should be clearly articulated in a "problem formulation" section that includes a full discussion of any highly exposed or highly susceptible subpopulations evaluated (e.g., children, the elderly, etc.). The questions the assessment attempts to answer are to be discussed and the assessment endpoints are to be well defined.
- The methods used for the analysis (including all models used, all data upon which the assessment is based, and all assumptions that have a significant impact upon the results) are to be documented and easily located in the report. This documentation is to include a discussion of the degree to which the data used are representative of the population under study. Also, this documentation is to include the names of the models and software used to generate the analysis. Sufficient information is to be provided to allow the results of the analysis to be independently reproduced.
- The results of sensitivity analyses are to be presented and discussed in the report. Probabilistic techniques should be applied to the compounds, pathways, and factors of importance to the assessment, as determined by sensitivity analyses or other basic requirements of the assessment.
- The presence or absence of moderate to strong correlations or dependencies between the input variables is to be discussed and accounted for in the analysis, along with the effects these have on the output distribution.
- Information for each input and output distribution is to be provided in the report. This includes tabular and graphical representations of the distributions (e.g., probability density function and cumulative distribution function plots) that indicate the location of any point estimates of interest (e.g., mean, median, 95th percentile). The selection of distributions is to be explained and justified. For both the input and output distributions, variability and uncertainty are to be differentiated where possible.
- The numerical stability of the central tendency and the higher end (i.e., tail) of the output distributions are to be presented and discussed.
- Calculations of exposures and risks using deterministic (e.g., point estimate) methods are to be reported if possible. Providing these values will allow comparisons between the probabilistic analysis and past or screening-level risk assessments. Further, deterministic estimates may be used to answer scenario-specific questions and to facilitate risk communication. When comparisons are made, it is important to explain the similarities and differences in the underlying data, assumptions, and models.
- Because fixed exposure assumptions (e.g., exposure duration, body weight) are sometimes embedded in the toxicity metrics (e.g., reference doses, reference concentrations, unit cancer risk factors), the exposure estimates from the probabilistic output distribution are to be aligned with the toxicity metric.

Source: EPA 1997c

Information on health status of local study populations is not usually readily available. With regard to cancer prevalence and incidence, yearly estimates are available on a national basis from the National Cancer Institute's Surveillance Epidemiology and End Results Project (e.g., Ries et al. 1998). Additionally, many States now maintain cancer registries consistent with National Cancer Institute recommendations. In order to provide some public health context for predicted cancer risks, relevant information from these sources will be accessed. Less information is available on the prevalence or incidence of other health effects. Federal public health agencies such as the Centers for Disease Control will be consulted. Rates for diseases as causes of death are available from the National Center for Health Statistics. Many States have